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Foreword

By special arrangement with the editors of the ARCHIVES OF OPHTHALMOLOGY, this issue is dedicated to Dr. Frederick Herman Verhoeff on his sixty-sixth birthday by his former students in recognition of his distinguished career.

Dr. Verhoeff was born on July 9, 1874, in Louisville, Ky., the son of Herman and Mary Jane (Parker) Verhoeff. His mother's family were of English descent and had settled in Kentucky. His paternal forebears were Dutch. His grandfather, Herman Verhoeff, fought with Blücher at the battle of Waterloo and was cited for bravery. He graduated from the University of Berlin and later brought his family to America in 1836, settling in Louisville. A son, Herman Henry Verhoeff (father of Dr. Verhoeff), became one of the community's foremost citizens, building the first grain elevator south of the Ohio River.

After graduating from Yale Sheffield Scientific School in 1895, Dr. Verhoeff attended Johns Hopkins Medical School, receiving his degree of Doctor of Medicine in 1899. The next two years were spent working in the Johns Hopkins Hospital and at the Baltimore Eye, Ear, Nose and Throat Hospital. Right at the start of his career he manifested such a special interest in ophthalmic pathology that in 1900, at the recommendation of Professor Welsh, he was called to Boston to take charge of the laboratory at the Massachusetts Eye and Ear Infirmary.

In 1902 he received his degree of Master of Arts at Harvard and then went abroad to study at the Royal London Ophthalmic Hospital (Moorfields) and some of the continental centers. Returning to Boston in 1903, he resumed his work as pathologist at the Massachusetts Eye and Ear Infirmary. His ability as a clinician and surgeon was as great as his ability as a pathologist, and in addition to his laboratory work and growing private practice, he worked up through the clinical grades at the hospital, becoming assistant ophthalmic surgeon in 1905 and succeeding to the position of full surgeon in 1913. In 1925 he received the additional title of chief of ophthalmic research. With the establishment of the Howe Laboratory of Ophthalmology in 1931, Dr. Verhoeff gave

up his position of pathologist and surgeon to assume the directorship of this new department and became consulting chief of ophthalmology at the hospital.

Concurrently with his hospital work, Dr. Verhoeff has been actively connected with the Harvard Medical School for the past forty years, becoming professor of ophthalmic research in 1924, a position which he still holds.

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During the World War he was commissioned a major in the medical corps of the United States Army and was stationed at Camp Devens, where he was in charge of ophthalmologic work.

A member of local and national medical societies, his qualities of leadership have been recognized by his election to the presidency of the New England Ophthalmological Society in 1920, to the chairmanship of the Section on Ophthalmology of the American Medical Association in 1932 and to the presidency of the American Ophthalmological Society in 1937. In 1921 at the meeting of the Section on Ophthalmology of the American Medical Association, he was presented with the Hermann Knapp Medal in recognition of his original paper "Gliomas of the Optic

Nerve." In 1930 he received the Ophthalmic Research Medal of the American Medical Association. In 1932 he was awarded the Lucian Howe Medal of the American Ophthalmological Society in recognition of his distinguished service to ophthalmology.

Dr. Verhoeff has been a frequent contributor to scientific journals. Since his first publication, in the *Bulletin of the Johns Hopkins Hospital* the year he graduated from medical school, he has published close to 200 papers on ophthalmology. In going over this list one cannot help being impressed with the wide variety of subjects. At first his contributions dealt chiefly with optics, muscle balance and refraction. Then followed numerous papers on pathologic and clinical subjects. Surgical procedure and new operations dominated his writings at a later period, and more recently, physiologic optics and binocular vision have been the favorite topics.

A regular attendant at medical meetings, he has not only presented many original contributions but has greatly enhanced the scientific value of the assemblies by his discussions of the papers of others. It has been truly said, "Woe unto a speaker who is not sure of his ground when Dr. Verhoeff is present." And yet his discussion, although often critical, is tempered with a sense of humor and an obviously sincere desire to bring out the truth.

No biographic sketch of Dr. Verhoeff would be complete without a word about his love of tennis. For more than forty years he has played this game regularly, summer and winter, and many of his fellow ophthalmologists have great respect for his ability on the courts. Even today his competitive spirit remains undulled, and his interest in the game is as keen as ever.

His intellectual honesty and his never failing willingness to help interns and others with their problems have endeared him to the institution with which he has been so long identified. His former students consider it a privilege as well as a pleasure to dedicate this volume to him.

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SOME FUNDAMENTAL PHYSIOLOGIC PRINCIPLES IN STUDY OF THE VISUAL FIELD

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Perimetry is the topographic and quantitative study of sensibility in the visual field. The generally used classification of perimetry as so-called qualitative and quantitative perimetry is not fully definitive or accurate. The distinction between these two classes of perimetry lies entirely in the use of chromatic stimuli in the former and achromatic stimuli in the latter. Both are fundamentally quantitative in this sense, for in order to make a study of the field the stimulus in either case must be varied in quantitative value, by varying its brightness or by varying its size.

In place of this somewhat misleading nomenclature, I prefer to consider study of the visual field under the two fundamental divisions: (1) topographic and (2) quantitative. Topographic perimetry refers to the study of the variation of sensibility throughout the field, while quantitative perimetry refers only to the study of the existing sensibility in relation to normal sensibility at any point in the field. Each division may be subdivided into achromatic and chromatic, according to the quality of the stimulus employed. Topographic perimetry furnishes the shape of the area in the field in which the sensibility is diminished. Quantitative perimetry furnishes the density of the defect in terms either of the just perceptible size of test stimulus or of the just perceptible brightness difference. In strictly scientific terms, the density could be more rationally expressed as the logarithm of the ratio of normal sensibility to the existing sensibility. Thus when the existing sensibility is the same as the normal sensibility, the ratio would equal unity and the logarithm of this, that is, the density, would be zero, indicating that no defect is present.

My classification is based on the consideration of those aspects of field defects which are of primary diagnostic and clinical importance, that is, the shape of the area of defective vision and the degree of the loss of perception in the area. Whether the defect exists for only achromatic or chromatic stimuli, or both, or disproportionately for both, is fundamentally only a question of the degree of loss of visual perception.

Normally, the factors that determine sensibility in the field of vision are optical, topographic and adaptational. There are inherent differences between persons, especially for the various chromatic stimuli. The

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optical factors include the refractive error, both axial and that due to oblique incidence of light rays from the peripheral field on the refracting surfaces of the eye, the pupillary area and its diminution with oblique incidence of light rays on the pupillary plane and the transmission of light by the ocular media.

The topographic factors that influence the field include variations in anatomy and physiology throughout the retina and variations in the optical factors in different parts of the field. Adaptational factor refers to the degree of background light stimulation.

The standardization of the normal field should take into account all the normal variations attributable to the aforementioned factors. It would be a tremendous task, however, to do this for a large series of normal subjects for both chromatic and achromatic stimuli and for a satisfactory range of adaptational conditions. The standards now referred to as normal have been obtained mostly from careful studies of a few normal subjects. The adaptational conditions, the brightnesses of the test stimuli, the pupillary apertures and the exact refractional states of the subjects have not been uniformly or generally specified. It is true that these accepted standards of normal all fall within certain limits. They generally have been selected because the intelligence, understanding and cooperation of the subject have been of a high degree, thus permitting a high degree of reliance to be placed on their responses, but also because the eyes of the subjects have been considered representative of normal, both with respect to pupillary and retinal function as well as to optical condition. These standards thus do not represent truly the average normal and do not indicate the range of normal but represent what is clinically almost an ideal normal.

Although there have been no comprehensive determinations showing the range of normal variations caused by the aforementioned optical, topographic and adaptational factors, the general effects of these factors on the topographic and quantitative aspects of the normal field should be recognized, as such knowledge will frequently aid materially in the study and interpretation of the visual field. As will be brought out later, the adaptational factor, by virtue of a differential effect on central and peripheral sensibility, can be used to advantage in increasing the delicacy and accuracy of studies of the central and paracentral fields.

In my opinion the most important single aspect of the physiology of the visual field is the change of sensibility with change of position of the test stimulus in the field, which I shall call the field gradient of sensibility. It concerns both achromatic and chromatic sensibility and topographically applies to a change of position in any direction in the field. It has been given hardly more than academic mention in works on study of the visual field, and its importance apparently has never been fully realized or explained.

Normally, the field gradient of sensibility is determined by the three classes of aforementioned factors. Of these, the optical and topographic cannot be altered, except so far as pupillary dilatation or contraction allows or excludes, respectively, optical aberrations arising from the peripheral zones of the lens. Only between wide limits of dilatation and contraction of the pupil would the difference in the amount of light admitted be of any significance as an adaptational factor. The effect of marked miosis on the visual field is especially noticeable in cases of chronic simple glaucoma in which the pupil is contracted as the result of using miotic drugs.

The effect of ametropia on the quantitative study of the field is dependent on the relation between the size of the retinal image and the differential threshold. With a given background brightness, the differential field sensibility, that is, the ratio of the background brightness to the just perceptible difference in brightness between the test object and the background, increases with increasing size of the test object. From experimental determinations that I have made, this relation may be expressed empirically by the following equation, in which S is the differential sensibility, D is the diameter of the round test stimulus in millimeters per meter distance from the eye and a and b are constants whose values depend on the eccentricity of the test stimulus in the visual field and the level of background brightness to which the eye is adapted: $\log S = a + b \log D$.

Since ametropia causes an increase in the size of the retinal image and a decrease in its brightness, the test stimulus will be perceived as long as the intensity of its blurred retinal image does not decrease to below the threshold, as expressed in the aforementioned equation, for the existing size of the latter. Since the proportionate effect of the blur circles caused by ametropia on the size of the blurred retinal image is less the greater the size of the test stimulus in the field, the effect of a given degree of ametropia would be less with larger than with smaller test stimuli.

In order to show the relative effects of various degrees of ametropia and of various sizes of test stimulus on the differential field sensibility, I calculated the latter in various degrees of axial myopia in the Gullstrand eye for several sizes of test stimulus, utilizing the aforementioned equation. The curves expressing the results are shown in chart 1*a* and *b*. The former represents the results with a background brightness approximating that of the illuminated arc of the Ferree-Rand perimeter and the latter the results with a background brightness approximately one-two hundred and fiftieth that of the former.

It is apparent from these curves that the larger the test stimulus, the greater is the field sensibility for a given degree of ametropia and the less is the difference between the field sensibilities for different degrees

of ametropia. Although the curves were calculated for the area of the field corresponding to the fovea, similar, although not necessarily parallel, results would be expected for ametropia of all kinds in other parts of the field. It is also apparent that in addition to the effects of varying the size of the test stimulus there is a decided difference in the slopes of the curves for the high and the low background brightnesses. With the low background brightness there is much less change in the differential field sensibility with increase in ametropia than with the high background brightness.

In computing these graphs, the test stimulus was taken as being at 1 meter from the nodal point, so that it is in sharp focus on the retina

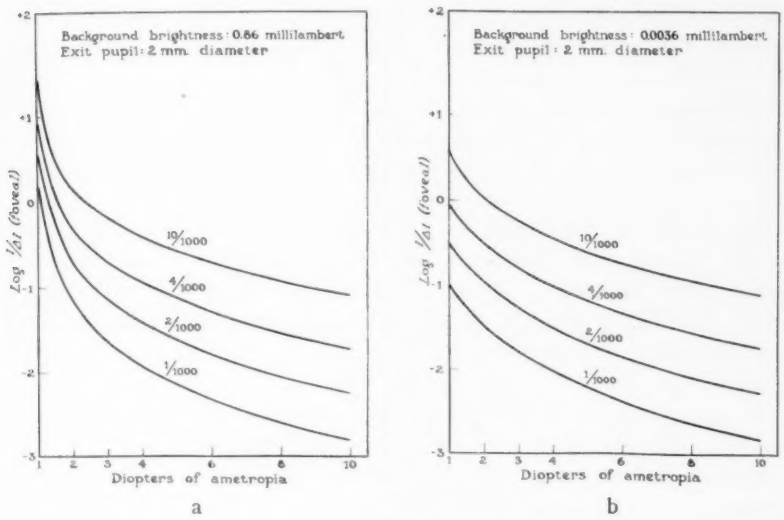

Chart 1.—Graphs showing the relative effects of various degrees of ametropia and of various sizes of test stimulus on the field differential sensibility in adaptation to high (*a*) and to low (*b*) levels of background brightness.

with 1 diopter of axial myopia. From chart 1*a* it is evident that with the same brightness difference as the differential threshold for a 1 mm. test stimulus at 1,000 mm. with 1 diopter of myopia, approximately a 10 mm. test stimulus at 1,000 mm. would be required for differential perception with 2 diopters of myopia. This appears to be a tremendous difference in the light of what is usually considered an adequate increase in size of the test stimuli in a clinical study of the visual field. The explanation of this, however, is that clinically the smallest test stimuli are usually much larger or much brighter than threshold stimuli, so that for small degrees of ametropia either little or no increase in their size or brightness is necessary to keep them at or above threshold values. It is interesting, in this respect, to compare for the same field differential thresholds the increases in size of the test stimuli necessary with given

increases in ametropia in chart 1*a* and *b*. The necessary increases are much less with the low than with the high background brightness.

The field gradient of sensibility has been defined as the change in field sensibility with change in position of the test stimulus in the field This change in position of the test stimulus in the field may be in any direction. It is simplest to represent the positional changes in a radial direction thus in terms of degrees of eccentricity measured from the fixation point along the various meridians. Along an isopter of the field the gradient of sensibility, of course, is equal to zero. The shapes of the isopters and their distances apart indicate in a general way the variations in the meridional gradients of sensibility throughout the field.

The more nearly circular shape of the paracentral isopters, having the fixation point as their common center, indicates the absence of any significant differences in the various meridional gradients of sensibility in this region.

The factors that normally determine the field gradient of sensibility are optical, anatomic and physiologic. The optical factors cause distortion, blurring and decrease in intensity of illumination of the retinal image of the test object as the latter is moved eccentrically in the field. The magnitude of the effects of these optical factors is generally not accurately determinable and, moreover, might be expected to vary considerably from one subject to another. In the central and paracentral parts of the field, however, their effects are least and, I think, can be regarded as insignificant in comparison with the effects of the anatomic and physiologic factors.

The latter factors comprise the distribution and relative densities of the cones and rods throughout the retina and the differences in cone function and rod function. According to the now well elaborated duplicity theory, the differential sensibility referable to the cones increases more rapidly than and above that referable to the rods with increasing brightness above a certain level. With decreasing brightness below this level, however, the cone sensibility decreases much more rapidly than and below rod sensibility.

Because of the different distributions of rods and cones, their respective varying densities and differences in their aggregate behavior,[1] one would expect varying effects on the differential sensibility throughout the field at different levels of adaptation from light to dark. There should be some intermediate point in the level of adaptation, however, at which the sensibilities due to cone function and rod function are approximately the same and at which the meridional field gradient of sensibility has a minimal average value. From various determinations, this transitional level of adaptational brightness lies in the neighborhood

1. Wright, W. D., and Granit, R.: On the Correlation of Some Sensory and Physiological Phenomena of Vision, Brit. J. Ophth., 1938, supp. 9, pp. 7-80.

of 0.01 millilambert. With varying effects of summation throughout the field and different summative effects in rod and cone function, this transitional brightness would be expected to vary somewhat throughout the field and with different sizes of the test stimulus.

As I could find no report of any systematic investigation of the differential sensibility from the center to the periphery of the field for different sizes of test stimulus and for a range of adaptational brightness that would include the probable transitional brightness, I investigated this in a representative normal subject. The details of this investigation will be presented in another publication. Part of the results are illustrated in chart 2*a, b* and *c,* in which the logarithms of the field differential sensibility, $I/\Delta I$, are plotted as ordinates and the eccentricities of the test stimulus measured from the fixation point as abscissas. The curves *A, B, C* and *D* are for background brightness of 0.865,

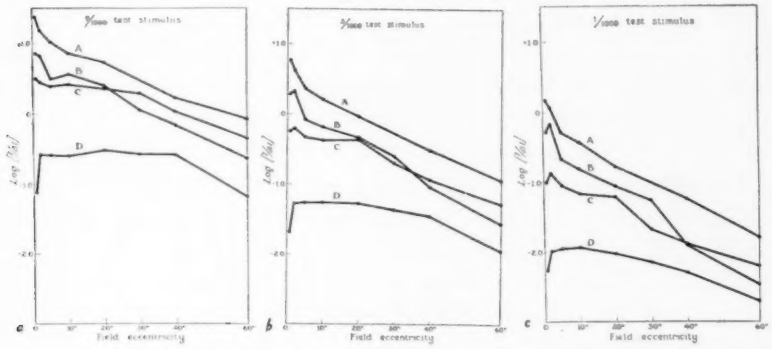

Chart 2.—Graphs of the meridional field differential sensibility in adaptation to various levels of background brightness for different sizes of test stimulus.

0.0343, 0.0036 and 0.0001 millilambert, respectively. Chart 2*a, b* and *c* is for round test stimuli of white light subtending, at 1 meter, angles of 9/1,000, 3/1,000 and 1/1,000 radian, respectively.

It is evident from these curves that there is the least difference between the differential sensibilities in the central and the paracentral field in the region of the adaptational brightnesses represented by curves *B* and *C,* namely, 0.0343 and 0.0036 millilambert, respectively. Curve *D,* however, reveals that the field gradient of differential sensibility in the paracentral and more peripheral parts of the field is least at the much lower brightness of 0.0001 millilambert.

Clinically, the field gradient of sensibility is significant chiefly in relation to the variation of density in field defects. Those that are not of the "punched-out" type generally have so-called sloping edges, that is, their density decreases as their limiting border is approached. The routine examination of the visual field is performed generally at a fairly

high level of adaptational, background brightness, so that the normal field gradient of sensibility would be comparable to that shown in curve *A*. The presence, for example, of a central defect of low density would then cause a depression of the first part of the curve. If one plotted the logarithm of the field differential sensibility against the retinal eccentricity in such a case, the density of the defect would be represented by the difference between this curve and the normal curve at any given eccentricity.

A central defect of uniform, but not absolute, density up to its border would simply cause a downward displacement, without change in slope, of the section of the curve corresponding to its extent. If the downward displacement, that is, the density, were great enough to lower the highest point of the displaced curve below the level of the normal curve just beyond the border of the defect, the latter, when the examination is performed with a test stimulus at the threshold of the normal bordering field, would appear to involve the whole of the meridian over the extent of the depressed part of the curve. But if the density were not great enough to lower the highest, or central, point of the affected part of the curve below the level of the normal bordering curve, then testing with a test stimulus at the threshold of the latter would reveal the defect falsely as a limited paracentral or peripheral scotoma. If all meridians were thus affected, the defect would be falsely represented as a pericentral annular scotoma. If instead of a test stimulus at the threshold of the normal bordering field one below the threshold of the most sensitive, the central, point of the defect were employed, the peripheral limits of the defect could not be determined.

Most defects, however, are not strictly of uniform density but instead have a nucleus of greatest density with progressively decreasing density outward from this to their limits. With such defects centering at the fixation point of the field, the graphs of the meridional sensibility, which normally would be comparable to curve *A*, would vary according to the density of the nucleus from those showing a gradual flattening at the apex to those showing virtually a crater-like depression over the extent of the defect with the sides of the crater gradually sloping up to the normal borders. In the first instance the defect could not be clinically demonstrated as a scotoma or circumscribed depression, and unless the quantitative aspect of the central and the paracentral field were examined, its presence could not be detected in the study of the visual field. In the second instance the total extent of the defect could be determined only by employing test stimuli at or very near the threshold of the bordering normal field.

In the case of defects that encroach on the field from the periphery, those of uniform density and practically vertical borders will cause uniform downward displacements of the curve of meridional sensibility.

With a normal meridional field gradient of sensibility, as in curve *A*, the only requirement for determining the limits and exact topography of such defects is the use of test stimuli at the threshold of the normal bordering field. This would necessitate the use of a graduated series of test objects in order to determine just which ones were perceived at their normal positions in the field. With peripheral defects that have sloping borders as they approach the center of the field, the same principle applies, although if the defect is found to extend close to the fixation point with decreasing density it becomes increasingly difficult to determine its absolute limits because of the much higher normal gradient of differential sensibility near the central region and the necessity of using very small or very weak test stimuli to meet the low differential thresholds there.

A steep gradient of differential sensibility would be indicated, in the usual examination of the visual field, by proximity of the isopters for a graded series of test stimuli and a low gradient by a spreading of the isopters. The closer together the normal isopters, the smaller is the zone of the field that can be examined by a given test stimulus with reasonable delicacy. The farther apart they are, the greater the region of the field that can be satisfactorily explored with the single test stimulus. It would thus facilitate and expedite the examination if the field gradient of normal differential sensibility could be as low as possible over a satisfactorily large zone of the field and if the test stimulus would approximate more closely to the average normal threshold of such a zone.

From chart 2 it is evident that by lowering the adaptational, background brightness to a certain level both of these problems can in a large measure be overcome. The meridional field gradient of differential sensibility can be significantly decreased so as to approximate an isoliminal state for the central and paracentral regions of the field, and at the same time the differential thresholds can be generally increased so that they are more closely approximated by the commonly used test stimuli.

In order to apply this clinically, a neutral tint Wratten filter of 3 per cent transmission was mounted in front of the aperture of a Bausch and Lomb tangent screen illuminator so that it could be readily swung in or out of the beam of light. With the filter in the beam of light, the estimated brightness of the tangent screen was about 0.003 millilambert from measurements made with the Macbeth illuminometer. Examination of the field was then performed in an otherwise dark room, about five minutes being allowed for the subject to become adapted to the reduced brightness of the tangent screen.

The subjects particularly examined by this method were those with central and paracentral scotomas and other defects, including homonymous hemianopia with so-called sparing of macular vision and early

glaucomatous defects, such as Bjerrum scotomas and Seidel signs. In all of such cases defects were definitely and strikingly brought out that either could not be demonstrated or were indefinite and doubtful by the ordinary methods of examination.

Definite central defects were demonstrable in some in cases in which the patients had subjective complaints suggesting their presence but in which the visual acuity was as high as 6/7.5, test objects as small as a 2 mm. red object at 1,000 mm. could still be recognized centrally and no defects were found with a 1 mm. white test object at 2,000 mm. with the ordinary method. In cases of glaucoma in which an early Bjerrum type of defect was detected in only the lower or upper half of the field with the ordinary examination, definite, unsuspected similar defects were found in the other, apparently normal half by examination in reduced illumination.

In 2 cases of lesion of the occipital lobe, 1 a case of verified glioma of the occipital lobe, in which typical homonymous hemianopias with sparing of the central field areas were found by the ordinary examination, the examination in reduced illumination with the 2 mm. white test object at 1,500 mm. demonstrated definitely that the hemianopias actually split the fixation areas centrally. This indicated that the homonymous macular fibers were not entirely spared but were affected along with the other homonymous field fibers. This presents a definite argument against the hypothesis of bilateral occipital lobe representation of the maculas and offers proof to substantiate the hypothesis of Rönne [2] that the explanation of so-called sparing of the macular field in such cases of homonymous hemianopia lies in the higher sensibility of this part of the field compared with the more peripheral portions. By making the central and paracentral regions approximately isoliminal, the sparing of the central portion of the field is shown to be only relative and not absolute, indicating the hemianopia to be actually complete but of decreasing density, up to the fixation point.

Although I have not had a suitable case in which to demonstrate it, I believe that, as is true of apparent sparing of the macular field, the so-called greater resistance of the macular fibers in conditions such as advanced chronic simple glaucoma with fields apparently contracted to within a few degrees of the fixation point is primarily an expression of the normally greater sensibility in the central field associated with adaptation to the higher levels of brightness.

In addition to the increased delicacy and accuracy of examination of the visual field in adaptation to the selected level of reduced illumination, this method also minimizes certain technical difficulties and, as

2. Rönne, H.: Ueber die Bedeutung der makularen Aussparung im hemianopischen Gesichtsfelde, Klin. Monatsbl. f. Augenh. **49**:289-312, 1911.

brought out in comparing chart 1*a* and *b*, reduces the effects of ametropia. A common technical difficulty affecting the ordinary examination is in mounting small test objects on wands so that the visibility of the latter is as small as possible. In order to make the wand as reflex-free as possible and blend with the black felt background of the tangent screen, I have devised wands coated with ground black velure. In the ordinary tangent screen illumination these wands are almost indistinguishable from the background when held properly so as to avoid shadows. In the selected reduced illumination they are entirely invisible against the background of the tangent screen, so that white beads mounted on them stand out on a uniform dark background. Also, in this level of brightness the larger test objects can be used, thus obviating the necessity of tiny, delicate test objects for refined examination.

Chromatic test stimuli, of course, provide a very sensitive method of examination. This, however, in my experience, appears to be simply because they are in general comparatively weak stimuli and not because the color sense is peculiarly susceptible to disease. This corroborates Traquair's [3] opinion. There is prevalent, however, the belief that disease of the epithelial layers of the retina causes a selective disturbance of the perception of blue, while disease of the neural-conducting system causes a selective disturbance of perception of red. I have searched in vain for reported evidence on which to base this belief. From my own experience with a large number of cases, I have been unable to confirm it.

The explanation of this fallacy, I believe, is in the fact that almost all cases of focal chorioretinitis and other retinal diseases that cause subjective visual disturbance and cause the patient to consult the oculist are macular or extend to involve the macula, while, except for retrobulbar or optic neuritis that causes central scotomas, diseases of the conducting mechanism generally cause either limited peripheral field defects or defects that in their early stages are densest in the periphery. In the case of central field defects, whether caused by local retinal lesions or lesions of the conducting mechanism, I have found perception of blue to be affected relatively early when the density of the defect is still too slight for loss of perception of white or red. This is because normally the central field area is less sensitive for perception of blue than for perception of red; consequently loss of perception of blue would be expected before loss of perception of red. In the periphery of the field, however, perception of red is normally weaker than of blue and, with slight defects in the periphery, loss of perception of red should be greater or occur earlier than loss of perception of blue. The colors to which I refer are, of course, the pigment colors of the test object and not spectral colors.

3. Traquair, H. M.: An Introduction to Clinical Perimetry, ed. 3, St. Louis, C. V. Mosby Company, 1938.

Although chromatic stimuli provide a sensitive means of quantitative examination of the field, they are inferior to the method of reduced illumination for topographic examination because of the fairly steep gradients of color sensibility and the reversal of the gradient for perception of blue on approaching the center of the field. In quantitative examination, they likewise provide a sensitive means of studying the density of defects. There so frequently occurs some form of color blindness, however, either typical red-green blindness or anomalous trichromatic vision, that the chromatic field study alone and so-called disproportion between defects for chromatic and achromatic study cannot be considered wholly reliable for diagnostic purposes without special studies of the color sense to determine the presence or absence of congenital dyschromatopia.

CONCLUSIONS

Study of the visual field is preferably classified as: (1) topographic and (2) quantitative, the former dealing with the shape and extent of field defects and the latter with their density. Either may be achromatic or chromatic, according to whether white or colored test stimuli, respectively, are employed.

Study of the visual field in the presence of uncorrected ametropia and refractional aberrations is more reliable with the use of larger test stimuli and lower levels of adaptational, background brightness.

A new principle, depending on the use of a selected low level of adaptational, background brightness, is presented. This method of examination is more delicate and accurate than the ordinary method of examination at relatively high levels of light adaptation and minimizes certain technical difficulties in refined examination.

Certain beliefs, which I consider incorrect, regarding the detection of field defects with chromatic stimuli are explained according to the normal physiology of color perception throughout the field.

ATOPIC CATARACTS

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In view of the fact that the crystalline lens is, embryonically speaking, a portion of the surface ectoderm, it would not be unusual for it to participate in some generalized disease or disturbance of the ectodermal layer. As any change in the crystalline lens must be a degenerative one, one might, therefore, expect cataracts to be frequently associated with dermatologic conditions; such, however, is not the case. Positive association of cataract with dermatitis is still uncommon in present day medical knowledge.

HISTORY

The literature on this subject is divided into two distinct groups: (1) articles describing the hereditary, familial and congenital cases, known either as cases of Rothmund's syndrome or of Werner's syndrome, and (2) articles describing cases of chronic dermatitis, usually associated with asthma and a marked history of allergy, and sometimes referred to as cases of cataracta neurodermatitis, cataracta dermatogenes, allergic eczema and cataracts and now "atopic cataracts."

Rothmund [1] in 1868 described a condition occurring in three families characterized by a telangiectatic condition of the skin which began in infancy and was complicated between the fourth and the sixth year of life by rapidly developing cataracts. In 1904 Werner [2] described a family of four members presenting the following syndrome: (1) ulceration of the lower extremities associated with sclerodermatous changes in the skin; (2) bilateral juvenile cataract; (3) precocious graying of the hair—canities; (4) changes of the larynx and voice; (5) hypogonadism; (6) constitutional physical inferiority, and (7) history of consanguinity. Vossius,[3] Guillain, Alajouanine and Marquézy,[4] Monier-

1. Rothmund, A.: Ueber Cataracte in Verbindung mit einer eigenthümlichen Hautdegeneration, Arch. f. Ophth. **14**:158, 1868.

2. Werner, C. W. O.: Ueber Katarakt in Verbindung mit Sklerodermie, Inaug. Dissert., Kiel, Schmidt & Klaunig, 1904.

3. Vossius, A.: Zwei Fälle von Katarakt in Verbindung mit Sklerodermie, Ztschr. f. Augenh. **63**:640-654, 1920.

4. Guillain, G.; Alajouanine, T., and Marquézy, R.: Sclérodermie progressive avec cataracte double précoce chez un infantile, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1489-1496, 1923.

Vinard and Barbot,[5] Bau-Prussak,[6] Sainton and Mamou,[7] von Arady,[8] Sézary, Favory and Mamou,[9] Krebs, Hartmann and Thiébaut,[10] Sézary and Mamou,[11] Russo,[12] Oppenheimer and Kugel,[13] Sannicandro[14] and Flandin, Poumeau-Delille and Perreau[15] all report cases, some 25 to 35 in number, of a syndrome similar to that described by Werner. Most of them are reported as cases of Rothmund's syndrome, but Oppenheimer and Kugel called attention to the fact that the condition did not resemble that in the cases reported by that author but, on the other hand, was typical of that described by Werner. Most of these authors are convinced that there is a disturbance of the endocrine glands, possibly a dysfunction of the parathyroids and possibly a pluriglandular condition. So much for this rare group of cases, so rare that only 2 are reported in the English literature.

In 1886 Vidal[16] clearly described a condition of young persons suffering from attacks of pruritus followed by thickening of the skin and lichenification, with a tendency for the condition to become worse during the fall and winter, with a positive association or alternation with asthma and usually with a constitutional background of unstable nervous tem-

5. Monier-Vinard and Barbot: Sclérodermie et cataracte. Syndrome familial, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:708-712, 1928.

6. Bau-Prussak, S. (Mme): La dégénérescence génito-sclérodermique, Rev. neurol. **33** (pt. 1): 316-322, 1926.

7. Sainton, P., and Mamou, H.: Hyperthyroidisme provoqué par la thyroxine chez un malade atteint d'un syndrome pluriglandulaire avec sclérodermie et cataracte, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1685-1690, 1927.

8. von Arady, K.: Ueber einige seltene Symptome der Sklerodermie, Ztschr. f. klin. Med. **106**:406, 1927.

9. Sézary, A.; Favory, A., and Mamou, H.: Syndrome tardif de sclérodermie avec cataracte associé à des troubles endocriniens, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:358-363, 1930.

10. Krebs, E.; Hartmann, E., and Thiébaut, F.: Un cas familial de syndrome de sclérodermie avec cataracte, troubles endocriniens et neuro-végétatifs associés, Rev. neurol. **1**:606-618, 1930.

11. Sézary, A., and Mamou, H.: Dermatoses et cataracte, Presse méd. **40**:1797-1799, 1932.

12. Russo, A.: Sindrome genito-sclerodermica e cataratia (morbo di Rothmund), Ann. di ottal. e clin. ocul. **62**:646-664, 1934.

13. Oppenheimer, B. S., and Kugel, V. H.: Werner's Syndrome, Tr. A. Am. Physicians **49**:358-370, 1934.

14. Sannicandro, G.: Neurodermite ed eritrodermia ittiosiforme congenita associate a cataratta (cataratta dermatogena), Arch. ital. di dermat., sif. **12**:84-104, 1936.

15. Flandin, C.; Poumeau-Delille, G., and Perreau, P.: Syndrome pluriglandulaire, maladie de Rothmund, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1184-1185, 1936.

16. Vidal, E.: Du lichen (lichen, prurigo, strophulus), Ann. de dermat. et syph. **7**:131-154, 1886.

perament. Besnier [17] in 1892 suggested the term prurigo diathesique; Brocq and Jacquet [18] in 1902, the term neurodermite diffuse; Coca [19] in 1932, the term atopy; Jülg [20] in 1934, the phrase allergic eczema on a constitutional basis; all of these were offered in an attempt to explain and clarify this condition. Returning to Coca's work, one finds his classification of allergic diseases, as follows: (1) atopy (hay fever, asthma and eczema), (2) contact dermatitis, (3) serum allergy and (4) drug allergy.

Coca elaborated the word atopy to express the peculiar hereditary tendency of certain persons to manifest untoward reactions to common protein materials, with the development of hay fever, asthma and eczema. Atopy implies the presence in the serum of the circulating blood of atopens or reagins, known as Prausnitz-Küstner bodies, which bodies possess the property of being able to convey a specific urticarial reacting sensitivity to normal skin to which they may be transferred.

Atopy is the base on which develops dermatoses from infancy to middle age; although immediate exciting factors vary, the fundamental predisposition is the same in all ages. This tendency to sensitiveness begins in embryonic life, continues through infancy and childhood and persists into adult life, tending to diminish in middle age. Sulzberger and Hill [21] admirably described this evolution of atopic dermatitis.

In infancy the dermatitis is oozing, weeping and crusty. In childhood and young adult life it consists of slightly elevated papules and diffuse, dry, scaly, hard and thickened, lichenified plaques. Often the papules and excoriations become secondarily infected, with oozing and crust formation.

The typical distribution in cases of moderate involvement is: flexual areas primarily, then the popliteal and antecubital fossae, face, forehead and front and sides of the neck. Generalized involvement exists in severe cases (figs. 1 and 2).

The course is chronic. Most patients have severe exacerbations with intervals of months or years between them; often some residue remains between the attacks. The seasonal aspect is emphasized, the condition being worse in cold weather. Change of environment has a striking effect

17. Besnier, E.: Première note et observations préliminaires pour servir d'introduction à l'étude des prurigos diathesiques, Ann. de dermat. et syph. **3**:634-648, 1892.

18. Brocq, L., and Jacquet, L., in Besnier, E.; Brocq, L., and Jacquet, L.: La pratique dermatologique, Paris, Masson & Cie, 1902, vol. 3, p. 141.

19. Coca, A. F.: Specific Diagnosis and Treatment of Allergic Diseases of the Skin: Present Status, J. A. M. A. **103**:1275-1277 (Oct. 27) 1934.

20. Jülg, E.: Ist es berichtigt, das Rostsche "spätexsudative Ekzematoid" aus der Gruppe der Ekzeme auszusondern? Dermat. Wchnschr. **99**:979-984, 1934.

21. Sulzberger, M. B., and Hill, L. W.: Evolution of Atopic Dermatitis, Arch. Dermat. & Syph. **32**:451-463 (Sept.) 1935.

in some cases. The opinion exists that eventually the disease runs itself out. The oldest patient in my series is R. L., 40 years of age.

Brunsting,[22] of the Mayo Clinic, reported 101 cases of atopic dermatitis in an excellent article, published in 1936. He found an equal distribution between the sexes, the youngest patient being 13 and the oldest 35, with an average age of 22. Seventy per cent of his patients gave a history of eczema in infancy, of hay fever or of asthma. Twenty-five per cent gave a history of continuous involvement since infancy or early childhood. Scratch tests were positive for 70 per cent of the 100 studied; many showed multiple positive reactions. An average eosinophil count of 9.7 per cent was found for the 50 persons studied.

About twenty-eight years after Vidal's description of this dermatitis, a Russian by the name of Andogsky[23] used the phrase "cataracta dermatogenes to describe bilateral cataract and dermatitis in a youth. In 1921 Davis[24] described the case of a youth 15 years of age, with rapidly developing cataracts, neurodermatitis and a long history of asthma. Ollendorff and Levy[25] in 1932, Gault[26] in 1933, Kirby,[27] Löwenstein[28] and Kurz[29] in 1934 reported the relation of cataracts in young persons with eczema. Kugelberg[30] in 1934 reported 2 similar cases and reviewed the literature, finding 18 previously reported cases. Daniel[31] in 1935 reported 3 cases of cataracts and eczema associated with marked allergy. Brunsting[22] in 1936 reported 14 cases, including in the 14 the 3 reported previously by Daniel. Some 30 cases are accounted for in the literature to date. This paper records 10 additional cases.

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Fig. 1.—*A* (case 1), close-up of the eyes of the patient in October 1937. *B* (case 1), appearance of the skin of the face. *C* (case 6), appearance of the skin of the face in November 1937. *D* (case 6), close-up of the eyes.

REPORT OF CASES

CASE 1 (fig. 1 *A* and *B*).—P. G., a woman aged 29, was first examined in the outpatient department of the Massachusetts General Hospital in 1925, at age of 15, because of hay fever and eczema. She was seen and studied in various clinics during the subsequent fourteen years and was hospitalized on two occasions for treatment of eczema, and on three occasions for operations on the eyes.

History of Atopy.—Eczema has been present constantly since infancy, with the usual flare-ups and remissions. Typical scaling and lichenification with excoriations, involving the face, neck, arms, legs and lower part of the abdomen, and marked pruritus occur. Treatment at various times has included restricted diet, ultraviolet irradiation, roentgen irradiation to various parts of the skin, inhalations of ethyl iodide, injections of sodium thiosulfate, injections of scales, administration of thyroid extract and attempted removal of proteins to which the patient was sensitive. Local washes and ointments are used frequently.

Asthma began in 1931, when the patient was 21 years of age, and has been present at intervals since then. Hay fever began in 1923, when the patient was 13 years old; there was some improvement after attempted desensitization with ragweed.

According to the family history, two of six siblings have asthma and hay fever; another has eczema. Both father and mother have had mild asthma. The mother's sister has hay fever and asthma (fig. 2).

Tests for cutaneous sensitivity to ragweed, birch, grasses, silk, histamine, orris, lamb, eggs, spinach, milk, house dust, horse hair, dog hair, cat hair, chicken feathers, human hair and staphylococcus protein gave positive reactions.

The eosinophil count was 5 per cent (only examination).

The eyes were normal and had a visual acuity of 6/6 in 1930. The vision in the left eye became blurred in August 1932, when the patient was 27. The visual acuity was 6/6 in the right eye and 6/30 in the left eye. Early posterior complicated cataracts occurred with many punctate opacities and iridescent crystals in the posterior and anterior cortices. The intumescent stage was reached in the left eye in December 1932. Cataract extraction was done on this eye. Glaucoma and prolapse of the iris occurred. The prolapse was excised, and iridotomy was performed. The visual acuity was 6/7 for three years, and finally complete separation of the retina occurred with vision limited to perception of light. Uncomplicated cataract extraction was done on the right eye in 1937, with a corrected acuity of 6/6, which has been maintained to date (1940).

History of Infection.—Frequent attacks of bronchitis occurred from infancy to 10 years of age. When the patient was 15 years old a roentgenogram of the chest was negative for tuberculosis, although there was some enlargement of the hilar glands. Roentgenograms of the sinuses were negative, and tonsillectomy was performed in 1925. A Wassermann reaction of the blood was negative. There was a secondary cutaneous infection at times, with a leukocyte count of 16,000 on one occasion. Secondary anemia with a hemoglobin content of 75 per cent is usually present.

Endocrine History.—The menses began at the age of 14 years and were irregular at times. Examination when the patient was 20 years old showed an infantile type of uterus. The basal metabolic rate was —5 in 1929, and the patient received thyroid extract for a time. There was no sugar in the urine. The blood sugar content was 94 mg. per hundred cubic centimeters in 1927. The blood calcium content was 10.57 mg. per hundred cubic centimeters and the phosphorus 2.56 mg. in 1932. The patient has always been underweight, roughly 15 to 20 per cent.

Dietary and Vitamin History.—A diagnosis of malnutrition and constipation was made in 1932. Much emphasis was placed on a diet high in vitamins. Many treatments with ultraviolet rays were given.

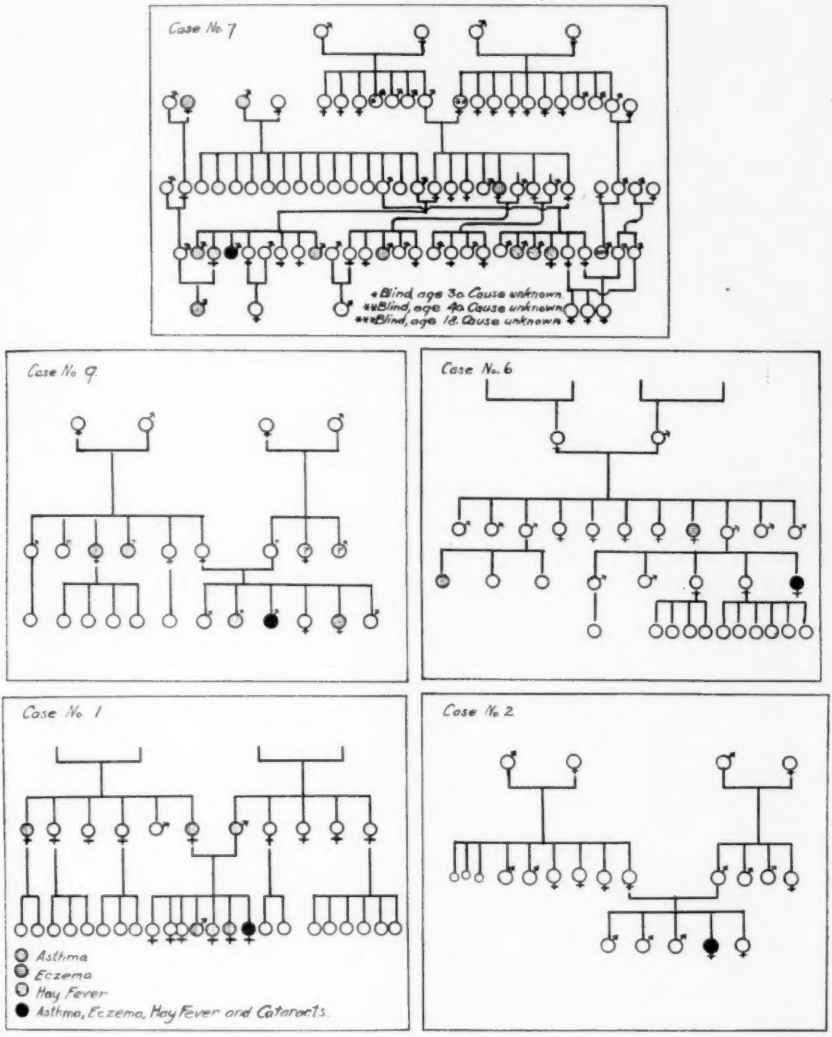

Fig. 2.—Heredity charts showing the occurrence of asthma, eczema, hay fever and cataract (cases 1, 2, 6, 7 and 9).

CASE 2 (fig. 3).—E. B., a woman aged 27, was first seen in the outpatient department of the Massachusetts General Hospital in 1931, at the age of 17, because of eczema of one year's duration. She was followed at regular intervals during the past eight years. She was hospitalized on three occasions for treatment of eczema and twice for treatment of the eyes.

Fig. 3 (case 2).—*A*, antecubital fossae in December 1935; *B*, the knees; *C*, the elbow; *D*, a close-up of the eyes in November 1937; *E*, face during exacerbation in December 1935, and *F*, the face during remission in November 1937.

History of Atopy.—Recurrent severe attacks of eczema occur with marked scaling and oozing, involving the head, face, scalp and all extremities; some eczema is present between severe attacks. Marked pruritus began when the patient was 16 years of age. Treatment varied and has consisted of dietary measures, removal from the diet of proteins to which the patient was known to be sensitive, injections of sodium thiosulfate, injections of scales, ultraviolet irradiation, injections of staphylococcus vaccine and the use of local washes and ointments.

The patient had influenza when 11 years of age, followed by bronchitis and asthma, which has been present at intervals since.

No history was obtained of asthma, hay fever, eczema, migraine or cataract in siblings, parents, uncles, aunts or grandparents (fig. 2).

Tests for cutaneous sensitivity to egg, casein, wheat, mackerel, oranges, chicken feathers, cat hair, dog hair, ragweed, orris, silk, staphylococcus protein and fungus protein were negative.

The eosinophil count varied from 4 to 14 per cent.

The visual acuity was 6/30 in each eye in 1931, when the patient was 17 years of age. There was a complicated posterior cataract in each eye. A congenital purulent central cataract was also present in each eye. Discussion and linear extraction of the cataract in the right eye were done with subsequent acuity of 6/6. The acuity in the left eye was finally improved by careful refraction to 6/12 and has been maintained to date (1939).

History of Infection.—The patient had influenza and bronchitis, followed by asthma, when about 11 years of age. Several abscessed teeth and the tonsils were removed. The Hinton test of the blood was negative. There was secondary anemia at one time with a hemoglobin content of 70 per cent. Leukocytosis was present, with a leukocyte count of 19,000, due to a secondary cutaneous infection on one admission to the hospital.

Endocrine History.—Catamenia began when the patient was 14 years of age and is regular and normal. The basal metabolic rate was —10; the patient received thyroid extract for some time. The thyroid gland was palpable, but it was finally decided that it was not involved. The patient is normally developed, although underweight by 10 to 20 per cent.

Dietary and Vitamin History.—Much attention was given to the diet, with emphasis on vitamins over a period of years. Treatments with ultraviolet rays were given.

CASE 3.—D. S., a woman aged 21, was first seen in the dermatologic clinic of the outpatient department of the Massachusetts General Hospital in 1932, when she was 14 years and has been followed at intervals since.

History of Atopy.—Infantile eczema was present till the patient was 14 months of age. Scaling eczema with some lichenification of the elbows, knees, hands and eyelids began when the patient was 14 years old and has remained to date (1940). Local washes and ointments were used, and injections of scales were given in 1932.

The patient has never had asthma.

The patient is an only child. The mother has hay fever. There was no history of eczema, cataracts or asthma, but a careful genealogy was not obtained.

Blurred vision was noticed in January 1935, when the patient was 17 years old. She was examined in the ophthalmic clinic in April 1935, with the following findings: visual acuity in the right eye, 6/30, due to early changes in the anterior cortex of the crystalline lens; mature cataract in the left eye with vision limited

to perception of shadows and good projection of light. The cataract in the left eye was extracted June 1936, with a subsequent corrected acuity of 6/6. No operation has been done on the right eye to date (1939).

History of Infection.—No history of infection was obtained. The Hinton test of the blood was negative.

Endocrine History.—Sexual growth was delayed. The menses began at the age of 16 years but are normal. The blood calcium content was 11.96 mg. per hundred cubic centimeters and the phosphorus content was 3.72 mg. There was no dysfunction of the parathyroids. The patient is underweight, about 10 to 20 per cent.

CASE 4.—M. F., a woman aged 23, was first seen in the outpatient department of the Massachusetts General Hospital in 1932, when 16 years of age, because of eczema. She was hospitalized on two occasions for treatment of eczema and several times for treatment of the eyes.

History of Atopy.—Eczema began when the patient was 2 years of age with lesions on the neck and arms and has continued to the present time (1940). The skin over the entire body is scaly, weepy and at times oozing; lichenification occurs in places and is constantly present. The patient is neurotic and spoiled; this was considered at one time to be a decided factor in bringing about exacerbations. Various treatments while she was under observation included dietary measures, injections of scales, psychoanalysis and the use of local washes and ointments.

The patient has never had asthma or hay fever.

The patient's only sister had eczema for a short time during childhood. The mother had eczema before she was married.

The patient was examined in the ophthalmic clinic in October 1933, when she was 17 years of age. The visual acuity was 6/60 in the right eye, and there was a posterior complicated cataract with many vacuoles in the anterior cortex. The visual acuity in the left eye was limited to perception of light; the eye contained a matured cataract and several posterior synechiae. Discission and iridotomy were performed on the left eye, with subsequent enucleation. Pathologic examination showed complete separation of the retina. The cataract in the right eye was extracted in November 1934, with a corrected acuity of 6/7.

History of Infection.—Secondary infection of the skin with enlarged cervical and axillary glands occurred on several occasions. The Hinton test of the blood was negative. The cutaneous tuberculin test was negative with a 1:10,000 dilution of tuberculin.

Endocrine History.—Catamenia began when the patient was 13 years of age and is usually regular and normal, although there was an unexplained amenorrhea of several months' duration at one time. A diagnosis of ovarian dysfunction was made, and estrogen was administered. The blood calcium content was 11.18 mg. per hundred cubic centimeters and the phosphorus content 2.86 mg. The patient is normally developed but much underweight, about 20 to 25 per cent.

Dietary and Vitamin History.—The patient had always been undernourished and uncooperative from a dietary standpoint.

CASE 5.—M. P., man aged 25, was first examined at the Massachusetts General Hospital in 1914, when 5 weeks old, because of severe infantile eczema. He was followed at frequent intervals in various hospital departments for past twenty-five years and was hospitalized on seven occasions because of eczema, once because of rheumatic fever and twice for operations on the eyes during this period of years.

History of Atopy.—The patient had severe infantile eczema when 5 weeks of age, thought to be due to milk. He has never been free from eczema since its onset; many exacerbations and partial remissions have occurred. Treatment of the eczema has consisted of the use of local washes and ointments, ultraviolet irradiation, inhalations of ethyl iodide, injections of scales and psychiatric advice.

The patient has never had asthma.

No history was obtained of hay fever, asthma or eczema in one sibling and a large number of uncles and aunts.

The eosinophil count was 10 per cent.

Completely negative reactions were obtained to some thirty or forty scratch tests in 1925. A slight reaction was obtained to horse hair at a subsequent test.

Blurred vision was noted in January 1935, when the patient was 19 years of age. He was examined in April 1933, when the corrected acuity was 6/5 in the right eye and 1/60 in the left eye. Early complicated posterior cataract was present in the right eye with many iridescent crystals in the anterior and posterior cortices. An intumescent cataract was present in the left eye with many vacuoles and iridescent crystals beneath the anterior capsule. A linear extraction was done on the left eye in May 1933; iridectomy was done on this eye in June 1933, because of secondary glaucoma. The right eye was not subjected to any operative treatment. The last recorded visual acuity was 6/6 in the right eye.

History of Infection.—The patient had chronic rheumatic fever at the age of 7 years and numerous attacks of impetigo contagiosa. Several abscessed teeth were removed when the patient was 18. The Hinton test of the blood was negative.

Endocrine History.—Development is normal, and the patient is sexually mature. The basal metabolic rate was —5. Examination showed no evidence of thyroid dysfunction. The patient has always been underweight, about 20 to 25 per cent.

Dietary and Vitamin History.—Numerous efforts were made to give the patient a diet high in vitamins. Many treatments with the ultraviolet rays were given.

CASE 6 (fig. 1 *C* and *D*).—R. L., a woman aged 40, was first examined in the outpatient department of the Massachusetts General Hospital in September 1935, when 35 years old, with a history of eczema of fifteen years' duration, asthma of twenty-seven years' duration and poor vision of four years' duration. She was hospitalized in 1936 for an ocular operation.

History of Atopy.—The patient has had scaly eczema with lichenification involving most of the body, face and legs constantly for fifteen years. The only treatment has consisted of the use of local washes and ointments, plus great stress on diet and elimination.

Asthma has been present with usual fluctuations for twenty-nine years.

One aunt and one niece have eczema (fig. 2).

Many scratch tests were performed in October 1938, with negative results.

Poor vision was first noted in the left eye when the patient was 31 years old. She was first examined at the ophthalmic clinic in October 1935, when she was 35 years old. The corrected visual acuity in the right eye was 6/20. The crystalline lens was clear; there was keratitis epithelialis, and marked corneal reflex involved the upper one third of the cornea. Projection of light was good in the left eye, and there was an almost mature cataract with a dense white plaque beneath the anterior capsule. Intracapsular cataract extraction was done in June 1936, with a corrected acuity of 6/6.

History of Infection.—Abscessed teeth were removed in 1938. The Hinton test of the blood was negative.

Endocrine History.—No special studies were made.

Dietary and Vitamin History.—Careful attention was paid to the diet for years with special emphasis on the rate of elimination. A diet high in vitamins was used. The patient has always been underweight, roughly 10 to 15 per cent.

CASE 7.—E. B., aged 29, was first examined in the outpatient department of the Massachusetts General Hospital in 1936, when 26 years of age. He was followed in the dermatologic and anaphylaxis clinics at frequent intervals and was hospitalized for cataract extraction in 1938.

History of Atopy.—Eczema began when the patient was 15 years old, at which time the family moved from the city to the country; it has been present constantly since. Typical scaling and lichenification occur. Treatment has consisted of the use of local washes and ointments, inhalations of ethyl iodide and dietary measures.

Asthma began at same time as the eczema and has continued with the usual fluctuations. Desensitization was attempted by injections of pollens.

Of six siblings, two have asthma and one has hay fever (fig. 2).

Positive reactions were obtained to cutaneous tests with timothy, ragweed, red top, plantain, orchard grass, milks, and yeasts, cat hair, dog hair, chicken feathers, silk and kapok.

An anterior polar cataract of the right eye was diagnosed in the ophthalmic clinic in February 1936; the left eye was normal. In 1938, a small dense dot was seen at the anterior pole of the right eye beneath the capsule, about 1 mm. in diameter; the remainder of the cortex was a diffuse milky white with the exceptions of a few pseudopod projections from the dense opacity. The left eye was normal and the crystalline lens clear. Intracapsular cataract extraction was done on the right eye in November 1938, with a corrected acuity of 6/5.

CASE 8.—P. R., a boy aged 4 years, was first examined at the Massachusetts Eye and Ear Infirmary when 14 weeks old, because of severe infantile eczema and cataracts. He was hospitalized on several occasions for ocular operations.

History of Atopy.—Severe scaly, oozing eczema of the face, scalp, arms, legs and upper portion of the body has been present since a few weeks after birth.

The father had infantile eczema.

There was a dense, white plaque beneath the anterior capsule in the visual axis; the lens was completely opaque. Both eyes were similar in appearance. Discission was done on each eye when the patient was several months old; it was repeated on each eye when he was 1 year old. Nystagmus and convergent strabismus of 20 degrees were present when the patient was 2 years old.

CASE 9.—P. D., a youth aged 16 years, was first seen in December 1938. He had been admitted to the hospital several times for operations on the eyes.

History of Atopy.—Eczema first occurred when the boy was 6 months old but soon disappeared. It recurred at the age of 1⅓ years, following a change of milk, and has been present since. It is always worse in the cold months. Various ointments and lotions were prescribed. Treatments with a sunlamp were given for long periods without relief.

The patient wheezes at times, but there are no definite symptoms of asthma. He has hay fever in the autumn.

Of five siblings, one has asthma and another asthma and hay fever. One uncle and an aunt have asthma (fig. 2).

Tests for cutaneous sensitivity were positive for eggs, ragweed and mackerel. When the patient was examined in 1938 it was found that vision had been failing in the right eye for one and one-half years and in the left eye for three months.

The right eye showed an intumescent cataract with a dense plaque opacity behind the pupil in the anterior cortex. A similar plaque was seen in the left eye with numerous streaks radiating from it and many punctate opacities and cholesterol crystals in the cortices; an early complicated cataract type of opacity was present at the posterior pole. Cataract extraction was done on each eye in 1939, with a corrected acuity of 6/6 in each eye.

History of Infection.—No history of infection was obtained.

Endocrine History.—Sexual development is normal, and the patient is about 15 per cent underweight.

Dietary and Vitamin History.—The patient always has had a good appetite. Eggs and mackerel have been omitted from the diet for the past five years.

CASE 10.—A man, aged 27, was first seen at the Massachusetts General Hospital at the age of 25, because of eczema.

History of Atopy.—Eczema occurred during infancy, and did not recur until the patient was 20 years of age. It has been constantly present since with frequent severe flare-ups. Treatment has consisted of the use of the usual lotions and ointments.

Asthma was present until the patient was 9 years of age. There were no siblings, and no family history of allergy was obtained. No tests for cutaneous sensitivity were done. Failing vision began at the age of 25 years. Usual acuity was 6/12 in each eye in 1937. There were dense anterior subcapsular plaques. Vision was 6/20 in the left eye in 1939. No operation has been performed to date (1939).

History of Infection.—The Hinton test of the blood was negative. A roentgenogram of the chest was negative for tuberculosis in 1938. A secondary infection of the skin occurred in 1937, with a leukocyte count of 25,000.

Endocrine History.—There were no symptoms or medical findings referable to the endocrine system. The blood calcium content was 10.08 mg. per 100 cc. and the phosphorous content 3.76 mg.

Dietary and Vitamin History.—The patient is slightly underweight but has a good appetite. No dietary restrictions were imposed.

THE CATARACT

Although Brunsting stated that the cataracts are distinctive, it is difficult to construct a typical picture from his and Benedict's [32] descriptions. Two types of lenticular changes can be described; the first is the typical and commonly seen complicated cataract. This usually begins at the posterior pole of the lens with increased iridescence, vacuoles and precipitates (fig. 4, A and B). Striation of the lens fibers is often present; small punctuate opacities are common, and iridescent crystals are frequent. These changes spread peripherally, and similar changes are soon noted in the anterior cortex, at the pole, immediately beneath the capsule. The changes progress, and the entire cortex becomes cloudy, forming an intumescent or a homogeneous mature cataract. In the cases reported here 10 of the 18 eyes showed lenticular changes of this type. These

32. Benedict, W. L., cited by Brunsting.[22]

changes are not to be distinguished from those found with uveitis, dinitrophenol poisoning, retinitis pigmentosa and separation of the retina, and, except that the cortex contains less of a granular, flocculent pre-

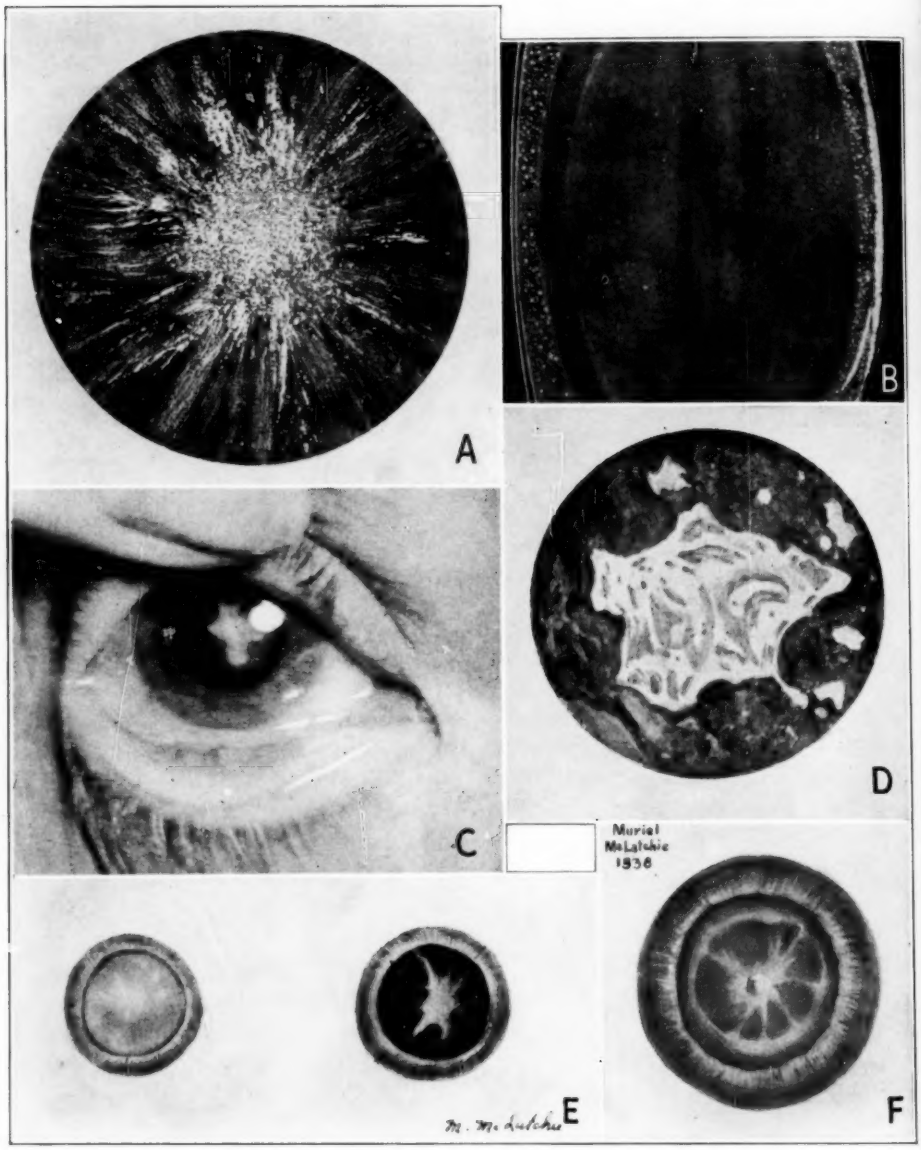

Fig. 4.—*A*, complicated posterior cataract posterior (from Vogt [33]); *B*, posterior complicated cataract and cortical punctate opacities (from Vogt [33]); *C*, photograph of an anterior cortical "plaque"; *D*, cataracta dermatogenes (from Vogt [33]); *E*, artist's drawing of cataracts with plaques (case 9), and *F*, artist's drawing of plaque cataract (case 7).

cipitate, from the cataracts found in young persons with diabetes, myotonia dystrophy and hypoparathyroidism. The second type cannot easily be named, but one finds it in Vogt's atlas [33] under the name "neurodermitis cataracts" (fig. 4, C, D, E and F). This type was found as a unilateral involvement on 2 occasions and a bilateral process on 3 others. This can be described as follows: a dense, irregular plaque of opacity in the anterior cortex, occupying the pupillary area immediately beneath the capsule of the lens and possibly involving it to some extent. Several authors refer to these as anterior polar and anterior capsular opacities. The changes are entirely cortical, with possibly some wrinkling and irregular elevation of a normal capsule covering the opaque and distorted cortex.

Histologic studies are available for cases 6 and 7. The lenses were removed intracapsularly, and microscopic sections show cortical degeneration with normal capsules. In 4 of these 8 eyes with subcapsular plaques the entire cortex was opaque, while in the remainder transparent cortex was present beneath the dense subcapsular plaque, as in Brunsting's cases.

It is interesting that unilateral involvement is frequent; this was found in 5 of Brunsting's cases and 2 of mine. Exception may be taken to including the infant in this series; the changes in the lens, however, were characteristic of the "plaque type," as proved by operation. Excluding the infant, the average age for the onset of cataract is 21 years; 19 years if the baby is included. Eczema precedes cataract formation by from one to nineteen years, and an average interval of twelve years exists.

COMMENT

Role of Allergy.—With due respect to allergy and the tendency to explain various conditions by it, one must admit that eczema and asthma are not readily explained on any other basis. One is therefore confronted with the possibility that the crystalline lens, as an ectodermal structure, might partake in the general reaction of hypersensitivity. Bilateral cataract might be expected, but such is not the case; in 30 to 50 per cent of cases unilateral involvement is present. This would mean that one lens becomes sensitized to some allergin while the other does not. Allan Woods, in his discussion of Daniel's paper in 1935, did not take kindly to the idea of "allergic cataract," although he did not hesitate to admit that he had never seen the association of dermatitis and cataract. He theorized that damage could occur to the lens capsule in the general reaction of hypersensitivity, thus permitting normal aqueous to enter the lens, producing an ordinary "traumatic cataract." At Woods' suggestion, aqueous was removed from the left eyes of patients 1 and 6, and

33. Vogt, A.: Atlas of the Slitlamp-Microscopy of the Living Eye, translated by R. Von der Heydt, Berlin, Julius Springer, 1921.

intradermal cutaneous tests were performed. Negative reactions were obtained. No specific allergin has yet been proved. The negative reaction obtained for these 2 patients does not mean that such an allergin does not exist.

Role of Diet and Vitamins.—The most striking feature from this angle is the almost universal tendency for these patients to be malnourished and underweight. One would estimate that for height, age and sex their weight was from 10 to 25 per cent below normal. This tendency is unexplained, as there was at no time any question of food scarcity. The metabolic rates, although normal, were low rather than high. Considerable attention has been given the diet of most of these patients; high vitamin intake has been emphasized, and foods to which patients showed positive cutaneous reactions were omitted. Many of these patients received ultraviolet irradiation during the period of years when this treatment was in vogue. No objective determinations of vitamin deficiency have been made.

Lack of vitamin B_2 in human beings produces a dermatitis which does not in the least resemble this eczema. Cataracts and dermatitis can be produced experimentally in animals by vitamin deficient diets;[34] satisfactory evidence that such is the case in human beings does not exist. Future investigations will be of great value in this respect.

Role of Endocrine Glands.—Hypoactivity or hyperactivity of the endocrine glands can account for various body changes, some of which are far from being clearly understood at the present time. One finds lenticular opacities reported in deficiencies of the pancreas, thyroid, parathyroid and gonads, and they are not very dissimilar either from some found in the "atopic cataracts." One would like to incriminate the endocrine changes of puberty, but this is not so easy with the average age for cataract formation as 21 years, unless one assumes that the changes have an insidious character. No striking disturbance of these glands was found in this group of patients. They are all sexually normal for age. Obesity is absent; in fact, the patients are underweight by about 10 to 20 per cent. Metabolic rates are within normal limits. The parathyroids cannot be blamed clinically or on the basis of blood calcium and phosphorus determinations. No evidence of diabetes exists in any of the cases. Clinically, the pituitary gland would not be considered, although no roentgenograms of the skull were taken in any case. The possibility of some pluriglandular disturbance cannot be denied.

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34. Mitchell, H. S.: Cataract in Rats Fed on Galactose, Proc. Soc. Exper. Biol. & Med. **32**:971-973, 1935. Yudkin, A. M., and Arnold, C. H.: Cataract Formation in Rats Fed on Diet Containing Galactose, ibid. **32**:836-837, 1935. Morgan, A. F., and Cook, B. B.: Cataract Producing and Dermatitis Producing Nutritional Factors, ibid. **34**:281-285, 1936.

Role of Autonomic Nervous System.—A disorder of the sympathetic nervous system has been considered by some as the basic feature; in fact, the term névrodermite was coined to satisfy this phase of the disease.[35] Many of these patients are rather unstable nervously, but one wonders which is cause and which is effect. It does seem reasonable to suppose that the irritation of the pruritis, the discomfort of the asthma, the disfigurement of the eczema and possibly the handicap of blurred vision would be sufficient to make any person sensitive, irritable and somewhat unstable. On the other hand, there is the suggestion that an instability of the sympathetic nervous system leads to a disturbance of circulation in the skin, which in turn makes an allergic disturbance possible. Many of these patients give the history of an exacerbation of symptoms following an emotional upset. Psychiatric advice and help have been sought and at times have been considered of some value, but once again one must not forget that the nature of this disease is one of marked fluctuation. It seems incredible to believe that a 14 week old infant could be subject to an abnormally irritable and hypersensitive nervous system sufficient to cause eczema and cataracts, and the mechanism as to how such a disturbance would bring about degeneration of the lens would be so complicated as to approach the fantastic.

SUMMARY

Atopy, a term coined by Coca to describe the occurrence of eczema, asthma and hay fever and lichenification of the skin in young persons with a constitutional predisposition to hypersensitivity, must include cataract formation as an uncommon addition to the syndrome. Ten cases are reported in detail. On 2 occasions intradermal tests were performed with aspirated aqueous, with negative reactions. Histologic examination of the crystalline lens in 2 instances showed cortical degeneration and normal capsule. The roles of infection, avitaminosis, deficiency of the endocrine glands and a disturbance of the autonomic nervous system as the causative factors in producing these cataracts are briefly discussed, but in my opinion they are much less attractive than an allergic (atopy) basis.

35. Alexander, A.: Neurodermitis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 6, pp. 371-445. Rasch, C.: Ueber Besniers Prurigo, Dermat. Wchnschr. **60**:72, 1915. Low, R. C.: The Eczema-Asthma-Prurigo Complex, Brit. J. Dermat. **40**:389-406, 1928. Drake, J. A.: The Asthma-Eczema-Prurigo Complex, ibid. **40**:407-414, 1928.

EFFECT OF LOCAL TYPHOID H ANTIBODY CONCENTRATION ON PRODUCTION OF CORNEAL ULCERS IN RABBITS

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In previous reports it was suggested that the presence of typhoid H antibodies within the eye, as demonstrated by titrating the aqueous, had an inhibiting effect on the production of experimental iritis. For the sake of convenience, the procedure was designated "interference" therapy.[1] This method was employed clinically by injecting varying dilutions of typhoid H antigen intravenously into patients with iritis and uveitis. In conformity with the experimental work, the aqueous was withdrawn by paracentesis of the anterior chamber, and the fresh aqueous richer in antibodies resulted in marked clinical improvement.[2] This procedure was also found to inhibit the rate of growth and spread of experimental staphylococcic corneal ulcers in rabbits.

It was thought to be of interest to note the effect of local antibody production in much higher concentration that could be produced by paracentesis after intravenous injection of the antigen. Typhoid H antigen has been used throughout, because it produced easily measurable antibodies in the blood and tissues and has been found effective therapeutically.

PRODUCTION OF OCULAR ANTIBODIES BY INJECTION INTO THE ANTERIOR CHAMBER

After local anesthesia was produced by the instillation of a 2 per cent solution of phenacaine into the conjunctival sacs of 10 rabbits, 1 minim (0.06 cc.) of a suspension of typhoid H antigen (25,000,000 to 1 cc.) was introduced into the anterior chambers of the right eyes. This created a mild local inflammatory reaction in the average animal. The reaction subsided in about two hours. This injection was repeated daily on five successive days. Six hours after each injection the aqueous was titrated; antibodies appeared as a rule after the third injection in an average concentration of 1:4. After repeated injections this rose to 1:6 on the tenth day. In fourteen days the concentration

1. Brown, A. L.: Experimental Uveitis: "Interference" Effect of Parenteral Administration of Proteins on Sensitization of the Uveal Tract, Tr. Am. Ophth. Soc. **33**:435, 1935.

2. Brown, A. L.: Uveitis: Rôle of Intraocular Typhoid-Antibody Content in Treatment, Am. J. Ophth. **20**:583 (June) 1937.

was 1 : 60. The ocular effect of these repeated injections varied greatly in the different rabbits. Every eye ultimately showed an inflammatory reaction, including ciliary injection and apparent photophobia. Each injection created a more violent reaction. After the fourth or fifth injection, the eye became reddened and the cornea steamy, with considerable exudate in the anterior chamber, and some of the eyes were lost through persistent inflammation with exudation of vitreous. The rise in the antibody titer of the aqueous was found to be relatively uniform in all the animals. Therefore, a fairly heavy suspension of attenuated live staphylococci, similar to that used to produce corneal ulcers in previous experiments, was used.[3] An attempt was made to inject a known strain into the superficial layers of the cornea which would always produce a fairly well developed, circumscribed corneal ulcer. These ulcers were to be produced in the rabbits at varying stages of the local ocular antibody concentration. Since a much higher intraocular antibody concentration would be produced by direct intraocular injection of the antigen and the staphylococcic ulcers could be produced at will, a reasonable control could be exercised over the antibody concentration to note the effect on the production of corneal ulcers.

EXPERIMENTAL PROCEDURE FOR PRODUCTION OF CORNEAL ULCERS

GROUP 1 a.—Fifteen fully grown rabbits were given injections of 1 minim of a suspension of typhoid H antigen into the right anterior chambers at intervals of twenty-four hours for three times. After the third injection the eyes were extremely irritable and were allowed to rest for five days. The average titer of the aqueous at this time was 1 : 4. On the ninth day 1 minim of a heavy suspension of live staphylococci was injected into both corneas in or about to the upper layers of the stroma of 5 rabbits. The remaining 10 were given another minim of typhoid vaccine into the right anterior chambers.

GROUP 1 b.—Seventeen days after the first intraocular injection of antigen, injections were made into the corneas of 5 more rabbits, as in group 1 a. The average titer of the aqueous of the eyes into which injections were made was 1 : 36; that of the aqueous of the left eyes (controls) was 1 : 2. The titer of the blood was 1 : 30. Since by my own observations and those of other observers [4] it was known that the titer in the ocular tissues would rise without further injection of typhoid H antigen, the last 5 rabbits comprising group 1 c were permitted to rest for four weeks.

GROUP 1 c.—At this time the titer of the aqueous of the 5 rabbits was found to have attained an average of 1 : 48. A suspension of live staphylococci was thereupon injected into both corneas of the animals in this group, in the same manner as in the preceding groups.

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3. Brown, A. L., and Pugh, J.: Effect of Intra-Ocular Concentration of Typhoid Antibodies on Experimental Corneal Ulcers, with Report of Seven Cases, Arch. Ophth. **16**:476 (Sept.) 1936.

4. Seegal, B. C., and Khorazo, D.: Method of Obtaining Undiluted Tissue Juice for Study of Tissue Antibody Titer, Proc. Soc. Exper. Biol. & Med. **31**:435 (Jan.) 1934.

The development of the corneal ulcers was watched daily, and the ulcers were classified as small, medium and large. Ulcers no larger than 1 mm. with barely raised surfaces were considered small; ulcers 1 to 2 mm. were considered medium, and those that were larger than 2 mm. with a considerably raised surface surrounded by infiltration and progressive erosion of the surface were considered large.

PROGRESS OF THE ULCERS

GROUP 1 a.—Two days after injection of the staphylococcus suspension 4 right eyes showed small ulcers, and all 5 left eyes showed similar lesions. Twenty-four hours later all ulcers were larger; 1 animal showed no ulcer in the right eye in the beginning and had none the entire time. The left eye of this animal, however, showed an ulcer comparable to those of the left eyes of the other 4. After the fourth day there developed a gradual difference in the size and characteristics of the ulcers of the right and of the left eyes. Those in the right eyes remained of medium size or small and were circumscribed, with no tendency to erode deeply into the stroma. Those in the left eyes were medium and 2 were large; all had small zones of infiltration, which indicated an advancing process. Two of the ulcers in the left eyes became considerably eroded on the surface, and the original organism was easily recovered on culture of the secretion. No mixed infection was discovered at this time. Later, culture of secretion from either eyes of various rabbits, especially those with large, ragged, eroding ulcers, showed some mixture, but the original organism was always the predominant one. On the fifth day the lesions in the right eyes of the 4 animals in group 1 a had become very small and circumscribed and were gone in eight days. The ulcers of the left eyes for the most part attained a size of 3 to 4 mm.; they became eroded in many cases and then began to retrogress. They contracted slowly and in two weeks left either faint nebulas or fairly deep scars, involving the superficial layers of the cornea and occasionally the stroma.

GROUP 1 b.—The right corneas of this group of rabbits were definitely more resistant to infection than those of the preceding group. Three days after inoculation with staphylococci, there were 2 right corneas with no lesions and 3 with very small ones. The lesions in the right eyes disappeared on the fifth day, leaving no trace. The left eyes were involved as in group 1 a.

GROUP 1 c.—The corneas of the rabbits in this group were inoculated five hours after the aqueous was titrated, as explained before. Two days after the inoculation there were well developed lesions in both eyes of all rabbits in this group. The ulcers in the right eyes had progressed to medium size on the fourth and fifth days and then remained stationary. There was little infiltration or erosion. The ulcers in the left eyes acted virtually the same as those in the preceding groups. Healing of the ulcers

in the right eyes was rather slow but faster than those in the left eyes. On the tenth day the ulcers in the right eyes had healed fairly well but left small nebulas, which involved the superficial layers of the corneas into the stroma. The ulcers in the left eyes healed as in the preceding groups.

EXPERIMENTAL PROCEDURE FOR THE PRODUCTION OF CORNEAL ULCERS IN THE PRESENCE OF HIGH INTRAOCULAR ANTIBODY CONCENTRATION

Fifteen new, well grown rabbits were given injections of typhoid H antigen of 1 minim into the right anterior chambers at intervals of three days for twelve times. After the third or fourth injection the eyes became extremely irritable, but the administrations were continued. In four weeks the titer of the aqueous of the right eyes averaged 1:60 and of the left eyes 1:2. The titer of the blood was 1:120. The second month the titer of the aqueous of the right eyes averaged 1:320 and that of the left eyes 1:2. The titer of the blood was 1:600. The third month the titer of the aqueous of the right eyes was 1:240 and of the left eyes 1:4. That of the blood was 1:1,200.

PROGRESS OF ULCERS

GROUP 2 a.—One minim of a suspension of staphylococci was injected into both corneas of 5 rabbits of the 15, as in the preceding groups. Three days after this inoculation small ulcers appeared in both corneas of all animals. On the third and fourth days there was a slow, practically equal growth of all lesions. By the sixth day the ulcers in the right eyes began to heal, but the eyes were very irritable. There was great circumcorneal injection and lacrimation. Exudate was present in the anterior chambers of 3 right eyes. The left eyes were not irritable but simply supported the growth of the ulcers as in the preceding groups. On the eighth day the ulcers in the right eyes were considerably smaller, and the eyes were somewhat quieter; the ulcers in the left eyes were healing more rapidly than those in the left eyes of the rabbits in the preceding groups. On the tenth day the ulcers in the right eyes were very small, but the eyes were still irritable. The left eyes were quiet, and the ulcers were gone, leaving slight nebulas. On the fourteenth day the right eyes were still irritable, and there were small nebulas marking the sites of the ulcers. Exudates in two anterior chambers had formed capsular membranes, obstructing the pupillary areas. The left eyes were quiet.

GROUP 2 b.—Two months after the initial injection of typhoid vaccine 5 more rabbits were given corneal inoculations of staphylococci. The third day the right corneas were very irritable, there was great ciliary injection, and exudate was present in the anterior chambers of all right eyes. Ulcers were well established and were larger than those in the left eyes. On the fourth and fifth days medium-sized ulcers were present

in the right eyes and very small ulcers in the left eyes. Ulcers in 2 right eyes by this time had become eroded and were apparently progessing rapidly. On the fifth day the ulcers in the left eyes were very small and the eyes seemed rather quiet. On the tenth day the ulcers in 4 of 5 right eyes were very large and completely surrounded by areas of infiltration. The ulcer in the fifth eye was smaller, but the eye was extremely irritable and highly inflamed, and the anterior chamber was filled with exudate. The ulcers in the left eyes were gone and the eyes were quiet.

GROUP 2 c.—Three months after the initial injections of typhoid vaccine into the anterior chambers, the last 5 animals were given corneal injections of staphylococci. The right eyes were extremely inflamed and reddened after the prolonged injections of typhoid vaccine. Six hours after the injections of staphylococci the 5 right eyes were more irritated, the pupils were contracting and there was a slight exudate in the anterior chamber of 1. The following day there were small ulcers in all the right corneas but none in the left. The second day the ulcers were well established and small but apparently progressing rapidly, because of the areas of infiltration surrounding them. There was only 1 left eye with a small established ulcer. The fourth and fifth days the ulcers in the right eyes had attained large sizes and were still progressing. The left eyes showed very small, circumscribed, clean-looking ulcers, which disappeared on the seventh day. The ulcers in the right eyes all eroded and broke down and in 2 instances destroyed the entire corneas by advancing almost to the limbus. On the eighth day these 2 ulcers perforated, and panophthalmitis ensued. The other 3 ulcers involved 4 mm. or more of corneal area, became completely eroded and after becoming thoroughly healed in fourteen days, left large scars which involved more than the middle stroma. These eyes, however, remained irritable, and the anterior chambers were filled with exudate and remained so until the animals died two or three months afterward. The eyes were sectioned and showed complete inflammatory destruction throughout, including gross corneal scars involving three fourths of the depth of the cornea in the centers.

COMMENT

The foregoing experiments not only indicate that an increased intraocular typhoid H antibody concentration inhibits the growth of ulcers produced by corneal injection of staphylococci but that there is probably an optimum concentration for this inhibition. This optimum seems to lie between a concentration of 1:36 and 1:60 as measured in the aqueous. A concentration beyond this up to 1:120 seems superfluous and beyond that has a deleterious effect on the structures of the eye and their resistance. Naturally, one must take into consideration the trauma produced by the needle at frequent intraocular inoculation and the toxic action of the antigen. The antigen as directly introduced into

the eye undoubtedly caused 90 per cent of the irritation and inflammation, because 1 mm. of sterile water was injected by means of a sterile needle into control eyes at the same time that the injections were made into the right eyes. The left eyes showed nothing but a mild temporary irritation from the procedure. It was evident that the more injections of typhoid H antigen were given and the more ocular irritation that was produced therefrom, the less corneal resistance there was to the growth of the staphylococcic ulcers. Since a fairly rapid increase in the titer of the blood can be accomplished by intravenous administration of typhoid antigen and an increased titer of the aqueous produced by paracentesis, up to 1 : 36 within six to seven days, it seems reasonable to conclude that this safe method is the only one applicable for clinical cases in which this method of therapy is used.

RETROBULBAR NEURITIS

OBSERVATIONS ON ONE HUNDRED CASES

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Data on 100 patients with retrobulbar nueritis, seen in clinic and private practice during a four year period and personally examined and studied by me, form the basis of this report. Not included in the series but observed during the same period were 65 patients with "toxic" amblyopia associated with deficient diets or with the use of tobacco or alcohol. The retrobulbar neuritis of such persons has distinct characteristics and can usually be readily differentiated from the condition which is the subject of this report. Also excluded were persons with toxic amblyopia produced by known toxic agents, such as lead, arsenic and thallium.

In an effort to establish an etiologic diagnosis whenever possible, almost all of the 100 patients were given complete neurologic and medical examinations, including Wassermann tests of the blood, examinations of the spinal fluid, dental and otolaryngologic consultations and roentgenographic examination of the skull, sinuses and teeth; tests for allergy and other special examinations were made when indicated. The complete records for all patients observed at the Vanderbilt Clinic or the Neurological Institute, many of which covered observations made over a period of years, were available for study.

The average age of the patients in this series when first examined because of blurred vision was 32.7 years, the youngest patient being 7 and the oldest 70. (In contrast to this the average age of a series of patients with tobacco-alcohol amblyopia was found to be about 55 years.[1])

Fifty-four per cent of the patients in this series were females and 46 per cent were males.

Retrobulbar neuritis may be defined in simple terms as a neuritis involving the retrobulbar portion of the optic nerve. A description of the diagnostic signs and symptoms as observed in this series of patients follows:

DIAGNOSIS

Symptoms.—Vision: In most cases the patient noticed suddenly that the vision was decreased in one eye. Sometimes this was observed

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1. Carroll, F. D.: Analysis of Fifty-Five Cases of Tobacco-Alcohol Amblyopia, Arch. Ophth. **14**:421 (Sept.) 1935.

on waking in the morning and sometimes while working or playing. Characteristically the vision grew worse after the first change was noticed, but a few patients reported loss of sight in one eye or in both eyes with no further change or with subsequent slight improvement. A few patients stated that vision had decreased in both eyes gradually and at about the same rate. Seventy-eight per cent had both eyes involved at one time or another but often not at the same time, especially in the early stages of multiple sclerosis. The average period of observation for the whole group was three and one-third years, but for the patients with unilateral involvement it was less, and it is probable that some of the 22 persons with unilateral involvement would have been found to have the condition bilaterally later if they had been followed long enough.

Many patients complained of a large blindspot in the center of vision, and some, in whom such spots were bilateral, stated that they saw better in a dull light.

Pain: This would seem to be an important symptom. Twenty per cent of the patients volunteered the information that the involved eye was painful on movement; others admitted having pain when questioned. The eyeball was often tender to palpation. In some cases pain was present only when the eye was turned in one direction; sometimes it was referred to as "deep," or "behind the eyeball." One patient stated that she had pain on movement of the involved eye for two weeks before the onset of blurred vision. Others had severe headaches at about the time of onset. This was frontal and over the affected eye in some patients; it was generalized in others, and it occurred in patients in whom no sinus disease was revealed by roentgenograms or by examination. Occasionally the headache preceded the attack, but it usually occurred only during the acute stage.

The cause of the headaches can only be speculated on. It may be that in some of these cases there is a mild, localized meningeal involvement. Structures outside the optic nerve must be involved to account for pain on movement of the eyeball, and it seems possible that in the acute stage there may be an edematous process close to the optic foramen. A few patients complained of pain under ophthalmoscopic examination, and most of these had photophobia, an uncommon symptom.

Signs.—Vision: In most cases there was marked reduction in visual acuity in the involved eyes. Several patients lost even perception of light during the acute process. Some patients with scotomas complained of foggy vision even when their visual acuity was 20/20.

Fields: The characteristic field change was a central scotoma. Thirteen patients also had moderate contraction of the fields, and the central scotomas of several, especially those with Leber's disease, broke through to the periphery of the field. They tended to be pericentral, i. e., with the densest part at the point of fixation, but were sometimes centro-

cecal, and the scotomas of some of the patients with bilateral retrobulbar neuritis resembled the scotomas found in persons with tobacco-alcohol amblyopia. Numerous persons showed paracentral scotomas as vision improved. Several had ring scotomas, and 1 presented an arcuate defect.

Disk: In the early stages of the disease there was usually no change in the normal appearance of the disks, although blurring of the margins of the disk sometimes occurred, with hyperemia of the disk and occasionally a slight elevation. After a few weeks pallor of the optic nerve usually developed temporally. This was not always the case, however, even though central scotomas had existed for many months. One patient

Features for Differential Diagnosis

	Retrobulbar Neuritis	Tobacco-Alcohol Amblyopia	Tumor of the Brain
Age.....	Young adult; average age 33 in this series	Older adult; average age 55 in author's series	Any age
Sex.....	Probably slightly more common in women	Much more common in men	.....
History.....	Patient usually consumes little alcohol or tobacco	Patient usually consumes more alcohol or tobacco; diet often deficient in vitamin B	.....
Onset.....	Usually rapid	Always gradual	Usually gradual
Involvement of one eye or both eyes	Usually unilateral at onset; later often bilateral	Always bilateral at first examination	Unilateral or bilateral
Field defect..	Pericentral scotoma; densest part often at fixation point; may be centrocecal; may be contraction of field or breaking through of scotoma to periphery	Centrocecal scotoma; densest part usually between blindspot and fixation point	Usually hemianopic tendency; defect often stopping at midline
Pain.....	Pain on movement of eye; tenderness on palpation	None	Very rare
Treatment with vitamin B	Little or no value	Considerable value	.....
Recovery.....	Often prompt regardless of therapy; tendency to recur	Usually gradual; recurrence very rare	Progressive course unless tumor is removed

had a bilateral central scotoma and normal-appearing disks over a two year period of observation. On the other hand, once the temporal pallor had developed it tended to remain, even though the visual acuity became 20/20 and no traces of a scotoma could be found. General pallor of the entire disk was sometimes present in the late stages, even though the fields indicated that only the papillomacular bundle had been functionally involved.

Pupil: The pupillary reaction generally considered to be characteristic of retrobulbar neuritis, i. e., contraction of the pupil in response to light, followed by prompt dilation while the same stimulus is being employed, was lacking in some of the cases in this series. The unreliability of this reaction as a sign of retrobulbar neuritis was further indicated by its demonstration in several normal eyes.

DIFFERENTIAL DIAGNOSIS

The two most important conditions to be differentiated from retrobulbar neuritis are tumor of the brain and tobacco-alcohol amblyopia. The distinguishing characteristics of these three diseases are listed in the accompanying table.

Tumor of the Brain.—The possibility of tumor of the brain should be ruled out in every case of suspected retrobulbar neuritis, especially in the presence of quadrantic or hemianopic features. Careful studies of the visual field are, of course, of the greatest importance, and it is to be hoped that there are now few patients showing an upper bitemporal hemianopia at examination who, because of failing vision, have had tonsils and teeth removed and sinuses repeatedly operated on. A unilateral central scotoma may be the first sign of a neoplasm either primarily intraorbital or intracranial or metastatic to the optic nerve. One patient with unilateral retrobulbar neuritis, however, had a 15 degree hemianopic central scotoma extending from the blindspot to the midline.

Tobacco-Alcohol Amblyopia.—This condition, as differentiated from retrobulbar neuritis, is always bilateral, tends to occur in persons of an older age group, is much more common in men, is always associated with bilateral centrocecal scotoma, is gradual in onset and recovery, is not accompanied by pain on movement of the eyeball or by tenderness of the eyeball and is associated with a history usually indicating the consumption of tobacco or alcohol and the lack of adequate vitamin B in the diet.[2]

ETIOLOGY AND TREATMENT

Retrobulbar neuritis was associated in this series with the following diseases, listed in the order of frequency:

Multiple sclerosis	37
Leber's disease	9
Encephalomyelitis	8
Arachnoiditis	3
Vascular disease	3
Sinus disease	2
Syphilis	2
Postspinal anesthesia	1
Neuromyelitis optica	1
Etiology unknown	34
Total	100

Multiple Sclerosis.—This disease was found in 37 per cent of the patients, 26 of whom were women and 11 men. The diagnosis

2. Carroll, F. D.: Importance of Diet in the Etiology and Treatment of Tobacco-Alcohol Amblyopia, Arch. Ophth. **18**:948 (Dec.) 1937.

was usually based on the opinion of more than one neurologist in the presence of several or all of the following findings: absence of abdominal reflexes, positive Babinski reflexes, hyperactive deep reflexes, intention tremor, transient paralysis of extraocular muscles, scanning speech, impaired gait, disturbances of the sphincter muscles and hemiplegias or paraplegias. Several patients with no other apparent neurologic symptoms at the time of onset of retrobulbar neuritis admitted under questioning a transient numbness of the fingers, arms or legs; definite multiple sclerosis developed in most of them within a few years. Studies of the spinal fluid, done in every case, were of value only in a negative sense. Only 1 patient had the paretic type of colloidal gold curve, 5555432100, with a negative Wassermann reaction of the spinal fluid, which is generally considered to be suggestive of multiple sclerosis; an elderly patient who showed no evidence of multiple sclerosis during a four year observation period presented the same finding.

In this group the average period of observation from the time of onset to the last ocular examination was almost five years. Many cases in which the causation was first considered unknown were placed in the group of cases of multiple sclerosis as the years passed. Ordinarily there was acute retrobulbar neuritis in one eye, which rapidly improved within a few weeks regardless of treatment. Occasionaly the second eye became involved while the first one still had a scotoma. Most patients had recurrences; 1 had an attack in each of four years, 1932, 1933, 1935 and 1936. Another patient at the age of 12 had a cloudiness in the right eye which developed into total blindness in one day; the eye then began to improve and became normal in six weeks. At 16 he had a similar attack in the same eye; six months later this was repeated in the same eye, but a central scotoma remained. At 17 he had his first attack in the left eye with vision decreased to perception of hand movements; there were other evidences of multiple sclerosis. A history of vision failing in both eyes gradually is obtained infrequently.

When a cure has been discovered for multiple sclerosis, a cure will have been found for retrobulbar neuritis in many cases, but until that time it is important to remember the normal course of the disease in evaluating any therapy. Hospitalization during the acute attack has been advised by me, but some of the most rapid recoveries in this series of patients were made by those who were neither hospitalized nor treated. Fever therapy by intravenous inoculation of typhoid organisms has been tried, and injections of sodium nitrite were given in the past, but there is no convincing evidence that the course of the disease was affected by either procedure. Vitamin B, so helpful in treating tobacco-alcohol amblyopia, was found to be of questionable value: In several cases of retrobulbar neuritis associated with multiple sclerosis, which were seen early in their course, the condition grew progressively worse despite huge doses of vitamin B.

In the matter of recurrences, certain conditions, such as infection of the upper respiratory tract, physical or mental trauma, pregnancy and acute allergic episodes, seem to be predispositional [3] and should be avoided whenever possible.

Leber's Disease.—Nine patients with familial atrophy of the optic nerve were observed in 6 unrelated families. One family, followed for many years by Dr. J. M. Lilly of Fayettsville, N. C., had 7 members afflicted, 2 of whom came under my care. The age of onset varied from early childhood to late adult life, and it is important to realize that even in the same family this condition may develop at any age. It begins as bilateral retrobulbar neuritis, sometimes much worse in one eye than the other. One patient lost vision rapidly until only perception of light remained, but vision improved and for the past three years it has been 3/200 in each eye and there have been large dense central scotomas that connect with the upper nasal periphery.

The following congenital abnormalities were noted in the cases of Leber's disease in this series: (1) absence of lateral tarsal ligament, (2) cataracts and (3) malformation of the urethra. Many patients with this disease have other lesions in the nervous system, and some are mentally deficient; disseminated lesions may resemble those found in multiple sclerosis.

Large doses of yeast and other vitamin B preparations were administered to these patients without apparent benefit.

Encephalomyelitis.—Eight patients with retrobulbar neuritis had encephalomyelitis. The mildest and the severest of these cases are reported:

CASE 1.—H. H., aged 7 years, a patient of Dr. Raynold N. Berke, had pain on movement of his eyes, followed three days later by sudden decrease in vision. This grew worse over a period of one week, and when the child was first seen in the Vanderbilt Clinic vision in the right eye was limited to counting fingers at 1 foot and in the left eye to 20/200. He complained of a buzzing in his ears for two weeks and of severe headache for two days; his parents stated that he had vomited before breakfast for the previous three days. Both optic disks were elevated about 1 diopter. The fields were unreliable. Neurologic examination showed a bilateral Babinski and Chaddock sign, markedly diminished deep reflexes and decreased hearing on the right. Hemolytic streptococci were found in the throat, and the cervical glands were slightly enlarged and moderately tender. The dental consultant found a "very septic condition of the gums" and advised removal of several teeth. Before this could be done the vision had increased to 10/200 in the right eye and 20/30 in the left eye, and the field of the left eye showed a central scotoma. The infected teeth were extracted. An otolaryngologist advised tonsillectomy because of infected tonsils, but since the vision was improving this was delayed. Vision became 20/20 in each eye in four weeks. Tonsillectomy was performed a few

3. Putnam, T.: The Criteria of Effective Treatment in Multiple Sclerosis, J. A. M. A. **112**:2488 (June 17) 1939.

days later. The patient has been perfectly healthy for nearly four years; his vision now is 20/20 in each eye, and the fields are normal.

CASE 2.—W. E., aged 55, a patient of Dr. Gordon Bruce, had vision of 20/15 in each eye in April 1938. In June he noticed a "spot" in front of the left eye, and three weeks later, on examination, vision was found to be 20/30 in the right eye and 20/100 in the left eye; a central scotoma was found in the left eye. Vision decreased to 20/70 in the right eye and to counting of fingers at 6 feet (182 cm.) in the left eye. Pilocarpine was given by his local oculist to produce sweating, and vision improved to 20/30 in the right eye and 20/100 in the left eye. On July 1 vision had returned to 20/40 in the right eye and 1/200 in the left eye, and central scotomas were present. The patient stated that he had had hay fever for twenty-five years and that he was sensitive to several foods. Ten teeth had been removed eleven days previously, and a numbness of both sides of the face was attributed by the patient to procaine. He had been staggering for several days. He was placed on a dehydrating regimen because of the possibility that the neurologic condition might have an allergic basis, but this was of no avail. On July 21 a tingling sensation developed in all his extremities, and he complained of noise in the ears. He was admitted to the Neurological Institute, where a multiplicity of neurologic signs was found. The respiratory center became involved, and the patient died on August 1. Death came seven weeks after the first onset of ocular symptoms in an apparently healthy person. Autopsy showed areas of demyelination and inflammation in both optic nerves and in the pons. The diagnosis was disseminated encephalomyelitis.

Several cases of encephalomyelitis with retrobulbar neuritis occurred after infections of the upper respiratory tract and 1 during an attack of influenza.

Arachnoiditis.—Some cases of bilateral retrobulbar neuritis are probably associated with a localized meningitis and perhaps a localized encephalitis. How frequently this occurs is unknown. Two examples follow:

CASE 1.—In a patient bilateral central scotomas with contraction of the fields gradually developed, with vision of 8/200 in each eye. Over a period of three years he had had severe headaches, personality changes and decreased intelligence. The sputum finally became positive for tubercle bacilli, and it was felt that he probably had a localized tuberculous meningitis.

CASE 2.—A boy aged 12 years had a dermatitis due to poison ivy and at the same time noticed decreased vision. During the three years that he was observed, the vision decreased from 20/200 in the right eye and 10/200 in the left eye to 1/200 in the right eye and 4/200 in the left eye. The central scotomas became a little more dense and the fields a little more contracted. Whether or not allergy was a factor is unknown. Encephalograms showed gas in the cisternae interpeduncularis and chiasmatis, and the neurologic surgeon refused exploration on this basis. This may possibly have been an error, and in view of the recent optimistic reports [4] on the value of operation in chiasmic

4. Bollack, J.; David, M., and Puech, F: Les arachnoïdites opto-chiasmatiques, Paris, Masson & Cie, 1937. Vail, D.: Optochiasmic Arachnoiditis, Arch. Ophth. **20**:384 (Sept.) 1938; Syphilitic Opticochiasmatic Arachnoiditis, Am. J. Ophth. **22**: 505 (May) 1939.

arachnoiditis, surgical therapy should be carefully considered for chronic cases in which the freeing of adhesions around the chiasm has sometimes been of value.

Vascular Disease.—The patients in this not too well defined group were adults in whom a central scotoma developed which could not be explained on any other basis than vascular disease. Two examples follow:

CASE 1.—An active man, aged 44, a patient of Dr. John Macnie, was "getting in shape" by working hard with a pick and shovel prior to leaving on an exploring expedition. He suddenly noticed a blur in front of one eye, and examination showed a small central scotoma in that eye and vision of 20/70. The macula appeared uninvolved. Ten days later vision had returned to normal and has remained so for two years.

CASE 2.—In a patient, aged 53, a central scotoma suddenly developed in one eye. He had arteriosclerotic heart disease, moderate retinal arteriosclerosis and calcium in the carotid plexuses and pineal body, as demonstrated roentgenographically. Over a four year period his vision improved from 6/200 to 20/70. No macular changes were ever seen.

Syphilis.—Only 2 patients in this series had syphilis. Both had bilateral central scotomas, and 1 had slight contraction of the peripheral field as well. Both had 4 plus Wassermann reactions of the blood and spinal fluid. It is well to remember that multiple sclerosis or tobacco-alcohol amblyopia may occur in patients with syphilis and that these conditions may account for the central scotomas.

Sinus Disease.—The importance of sinus disease in retrobulbar neuritis is still a matter for controversy. In 2 cases in this series the retrobulbar neuritis was thought to be due to sinus diseases. One of these is reported as follows:

S. C., a man aged 56, had an infection of the upper respiratory tract and severe frontal headaches and a few days later, blurred vision in the left eye. Vision decreased rapidly and in two days became nil in that eye. The left sphenoid sinus contained a large amount of foul-smelling pus from which B. coli and Staphylococcus aureus were recovered. Examination six weeks later showed normal vision and a normal visual field in the right eye; vision in the left eye was nil, and there was atrophy of the optic nerve. Roentgenograms of the skull showed an osteitis of the bone surrounding the left optic canal. Neurologic, otolaryngologic and dental consultations indicated only pyorrhea and some residual infection in the sinuses.

Six patients of the 34 listed as having retrobulbar neuritis of unknown causation also had some evidence of sinus disease, and the retrobulbar neuritis may have been a result of it. The longer these patients are followed, however, the more often do other lesions develop in the nervous system and the less frequently does sinus infection seem to be the primary cause. The great majority of patients who finally arrive at the Neurological Institute with advanced multiple sclerosis

and a history of one or more attacks of retrobulbar neuritis have had at least one sinus operation, usually several. If definite sinus disease is present, however, I believe everything possible should be done to eliminate it just as any other possible source should be removed.

Postspinal Anesthesia.[5]—Only 1 per cent in this series had retrobulbar neuritis following spinal anesthesia.

I. G., a man aged 34, had an appendectomy under spinal anesthesia with procaine hydrochloride; six days later pain developed in the spinal region as well as headache and "buzzing" in the head. He stated that he was "almost blind for six days" and has had diplopia since that time. Visual acuity one month after operation was recorded as 20/200 in each eye and at one and one-half months as 20/40 and 20/50. When he was seen by me two and one-half months after operation, vision was 20/15 and 20/20; a residual paracentral scotoma was present in the left eye, and the patient still had a bilateral paralysis of the sixth nerve.

Neuromyelitis Optica.—One patient in this series had neuromyelitis optica.

O. L., a woman aged 49, was admitted to the Vanderbilt Clinic in 1935, complaining of decreased vision in the left eye and pain in back of that eye. Three months previously a hysterectomy had been performed with the patient under spinal anesthesia, and while in the hospital she noticed pain on movement of the left eye and tenderness to palpation. Vision on admission was 20/20 in the right eye and 20/50 in the left eye, and the fields showed an arcuate scotoma in the left eye below and involving the point of fixation. The possibility of the spinal anesthesia being a factor was considered. The patient was closely watched and the fields indicated that the scotoma was enlarging. After ten months a small upper temporal defect appeared in the other eye; at one year vision decreased in the right eye, and when the patient awoke one morning she was completely blind. A neurosurgeon whom she consulted immediately explored the chiasmal region. He wrote: "Markedly degenerated optic nerves were found with some definite thickening of the arachnoid around them. However, the rest of the brain appeared sclerotic and changed in color, so that the nature of her disease remained unsolved even after the exploration." On the third day postoperatively the vision began to return, and in two weeks it was 20/30 in the right eye and 6/100 in the left eye. The fields were moderately contracted. The patient maintained this vision and felt well for a year and then, two years after the onset of her condition, decreased vision, paralysis of both legs, weakness of the arms, numbness extending up to the chest, urinary incontinence and obstipation suddenly developed. A definite myelitis was present, and now for the first time the diagnosis of neuromyelitis optica was obvious. After hospitalization for a month the patient was discharged greatly improved. When she was seen nine months later vision was again 20/30 in the right eye and 20/200 in the left eye. Three years after the onset of the patient's symptoms myelitis with paralysis and loss of sensation in the lower extremities again developed. Drainage of the spinal fluid was performed for several weeks, and the patient improved once more but not completely. There were moderate weakness and numbness in her extremities, nystagmus was present and vision was reduced to 10/200 in each eye.

5. Brock, S.; Bell, A., and Davison, C.: Nervous Complications Following Spinal Anesthesia, J. A. M. A. **106**:441 (Feb. 8) 1936.

Unknown Etiology.—The patients in this group, with the exception of 2, were followed for slightly less than two years as compared with almost five years for the group with multiple sclerosis. The causes of retrobulbar neuritis of some of them might well have been determined if they could have been followed longer, but there would probably still remain a considerable number of cases in which origin is unknown.

1. One group of these patients presented the following characteristics: There was bilateral retrobulbar or optic neuritis [6] which became rapidly worse, so that vision might become nil in each eye within a few days. The history of a preceding infection of the upper respiratory tract was common. All other examinations gave negative results. Usually recovery started within a few weeks, but often there were permanent defects in the fields. Four of these patients became totally blind in both eyes within two weeks, and then the vision gradually improved. The present vision in these cases is: (*a*) 20/20 in the right eye and 20/30 in the left eye; (*b*) 20/30 in each eye; (*c*) 12/200 in each eye; (*d*) 20/40 in each eye. The patients were all young adults. Multiple sclerosis developed in 1 of them several years later, but this is not characteristic. The spinal fluid from 2 of these patients seen at the onset of blindness was injected into the brains of mice and into the anterior chambers of rabbits. The results were negative; no virus was demonstrated.

2. Allergy has been established as a definite cause of retrobulbar neuritis [7] and may have been a factor in some of the cases of this series. One patient had angioneurotic edema, often unilateral, over a period of years due to sensitivity to a variety of foods. Another had retrobulbar neuritis which developed several weeks after serum sickness. The evidence in several instances was suggestive but not convincing. The possibility of allergy should be considered in every case in view of the striking results which have been obtained in cases of allergy in which the offending substances have been eliminated.

3. The importance of infected tonsils and teeth and of other foci of infection is not known, but it would seem well to remove any such focus whenever possible.

SUMMARY

One hundred consecutive cases of retrobulbar neuritis personally observed by me are reviewed.

A guide to the differential diagnosis of this condition from tumor of the brain and tobacco-alcohol amblyopia is presented.

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6. Clay, G. E., and Baird, J. M.: An Unclassified Type of Optic Neuritis, Arch. Ophth. **18**:778 (Nov.) 1937.

7. Kennedy, F.: Allergic Manifestations in the Nervous System, New York State J. Med. **36**:469 (April 1) 1936.

The causative factors seemed to be multiple sclerosis in 37 per cent, Leber's disease in 9 per cent, encephalomyelitis in 8 per cent, arachnoiditis in 3 per cent, vascular disease in 3 per cent, sinusitis in 2 per cent, syphilis in 2 per cent, postspinal anesthesia in 1 per cent and neuromyelitis optica in 1 per cent. These etiologic findings were just what happened to occur in 100 consecutive cases and do not imply by any means that this is an average expectancy for the country or even for the community.

In 34 per cent of cases the cause was not determined.

If the etiologic agent is known, treatment should be directed toward its elimination. When it is unknown, treatment is of questionable value. Hospitalization during the acute attack is probably advisable. Certain conditions predisposing to recurrence in cases associated with multiple sclerosis should be avoided.

Retrobulbar neuritis is due to a large number of different etiologic agents, and every case should be studied as completely and over as long a period of years as possible.

ISOLATED CONGENITAL ABSENCE OF THE INFERIOR RECTUS MUSCLE

REPORT OF TWO CASES IN WHICH OPERATION WAS PERFORMED

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Isolated congenital absence of the inferior rectus muscle is rare. So great an authority as Bielschowsky [1] stated in a personal communication: "I cannot remember having seen a single case of an isolated congenital paralysis of the inferior rectus muscle. . . ." Further, I have been able to find less than 10 cases reported in the literature.

Whitnall,[2] on the basis of his experience in the dissecting room, expressed the belief that deficiencies and abnormalities of the ocular muscles are not as rare as would appear from a survey of the literature. He further stated that they arise from developmental errors in the cleavage from the common premuscular mesoblastic mass. In this, both Whitnall and Mann agreed. Peter [3] made the same generalizations.

According to Mann,[4] the four rectus and the two oblique muscles separate from their common mesodermal cone, which surrounds the back of the globe at the 20 mm. stage. The levator superioris muscle is not present at this stage but arises soon thereafter by separating from the medial border of the superior rectus muscle. Consequently, if the superior rectus muscle does not develop, the levator is necessarily absent. Another important muscular anomaly is absence of the external rectus muscle. Mann [5] further asserted that various causes can produce the final effect of a congenital ocular paralysis. In the literature may be found numerous accounts of anomalies of the extraocular muscles, the majority of which relate to the absence of a single muscle.[5a]

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1. Bielschowsky, A.: Personal communication to the author, Nov. 19, 1939.
2. Whitnall, S. E.: The Anatomy of the Human Orbit and Accessory Organs of Vision, ed. 2, New York, Oxford University Press, 1932, pp. 286-287.
3. Peter, L. C.: The Extraocular Muscles, ed. 2, Philadelphia, Lea & Febiger, 1936, p. 32.
4. Mann, I.: Developmental Abnormalities of the Eye, New York, The Macmillan Company, 1937, p. 405.
5. Mann,[4] p. 413.
5a. Howe, L.: The Muscles of the Eye, New York, G. P. Putnam's Sons, 1907.

Posey [6] in 1923 gave an excellent review of ocular motor anomalies. At this time he reported fairly completely the gross muscular anomalies of the eye which he gleaned from a review of the literature. He mentioned Krause, Ledouble and Lawford, who described the absence of the internal rectus muscle; Krause and Bahr, who called attention to the absence of the external rectus muscle; Seiler and Steinheim, who described the absence of the superior rectus muscle, and Davis, who described the absence of both inferior rectus muscles. Stieren [7] reported absence of the inferior rectus muscles. He freely incised the conjunctiva of his 6 year old patient, and did not find even the "slightest rudiment of an inferior rectus muscle." Both Harles [8] and Seiler have reported absence of the oblique muscles. Klinosch has described absence of all the ocular muscles.

McDannald [9] reported the occurrence of sursumvergence in a 31 year old man with absence of the left inferior rectus muscle (proved by operation). The patient was improved by tenotomy of the left superior rectus muscle and splitting of the internal and external rectus muscles with attachment of the lower half of each muscle to the lower section of the globe, a procedure first recommended by Hummelsheim (1907).

Natale [10] reported an interesting case of congenital strabismus in which congenital absence of the superior and inferior rectus muscles was found at operation. Posey [11] reported the case of a young man with congenital right hypertropia and facial asymmetry. The combined downward and outward motion of the right eye was absent, but the eye could be moved downward and inward to a certain extent by the superior oblique muscle. All other movements of the eyes were normal. Because of the deficiency of action of the right inferior rectus muscle, a Hummelsheim muscle transplantation operation was decided on and done. At operation the inferior rectus muscle was found to be absent except for a slight (?) rudimentary portion, which was found at the usual site of the inferior rectus muscle. Two weeks later 10 degrees of left hyperphoria and 20 degrees of esophoria for distance were found. There was normal vision in each eye with correction. Zentmayer,[12]

6. Posey, W. C.: Concerning Gross Structural Anomalies of Muscles of Eye and Adnexa, Tr. Am. Acad. Ophth. **28**:243, 1923.

7. Stieren, E.: Congenital Absence of Both Inferior Recti Muscles, Am. Med. **5**:581, 1903; cited by Stevens, G.: A Treatise on the Motor Apparatus of the Eyes, Philadelphia, F. A. Davis Company, 1906, p. 487.

8. Harles, H.: Absence of Obliques, Arch. f. Physiol. **4**:23, 1880.

9. McDannald, C. E.: Arch. Ophth. **43**:515, 1914.

10. Natale, A.: Congenital Ptosis and Muscular Anomalies of the Eye, Arch. de oftal. de Buenos Aires **4**:14, 1929; abstracted, Arch. Ophth. **2**:485 (Oct.) 1929.

11. Posey, W. C.: Congenital Hypertropia, Am. J. Ophth. **4**:524, 1921.

12. Zentmayer, W., in discussion on Posey.[11]

discussing this case, stated he had 1 case in his experience similar to this case of congenital hypertropia.

According to Hardy,[13] Coover [14] in 1909 operated on a woman in an attempt to advance what he thought were paralyzed superior and inferior rectus muscles and found them absent.

REPORT OF CASES

CASE 1.—*History.*—Miss E. H., aged 19, was referred to me on March 15, 1938, for treatment of a marked congenital right hypertropia (fig. 1 G). Deviation of the right eye was first noticed by her family in early childhood, and at the age of 4 years the parents noted as she would "look out of the corner of the right eye she could not look down." There was no history of diplopia, dizziness, vertigo or nausea.

The patient's general health had been excellent. She had varicella, pertussis and measles in childhood, and an appendectomy was performed in 1934.

There was nothing of significance in the family or social history.

Physical Examination.—The heart, lungs, abdomen and extremities were normal; abnormal findings were limited to the right eye.

Laboratory Data.—The blood pressure was 118 systolic and 60 diastolic. Urinalysis of one specimen revealed a slight amount of sugar. The fasting blood sugar, however, was only 78 mg. per hundred cubic centimeters. Other laboratory data were negative.

Ocular Examination.—Vision in the right eye with a —0.25 sph. ⊃ + 1.00 cyl., ax. 95 was 6/10; that in the left eye with a + 2.00 sph. was 6/5.

Except for the refractive error and muscular anomaly, the eyes were normal: the lids, cornea, anterior chamber, iris, pupils, lens media and retina were normal.

The following movements of the right eye were normal: The right eye deviated upward in the primary position from 10 to 25 arc degrees. The vertical deviation was somewhat greater at the near point; there were 3 prism diopters of exophoria for distance and 5 prism diopters of exophoria for near vision. When the patient looked to the left there was good binocular fixation, excellent stereoscopic depth perception. In the primary position there was never binocular fixation but always marked right hypertropia. The following movements up and to the left, to the left and down and to the left were well executed. As dextroversion took place, the right hypertropia rapidly increased. This was greatest when the patient looked down and to the right, as the right eye could not be rotated down below the midline. Her retinal correspondence was normal with the after-image test (foveal images), as is often the case in congenital deficiencies. Diplopia was easily elicited with a red glass, but when the patient looked in a field where binocular fixation was not possible suppression or replacement easily took place (fig. 1).

On April 13 the patient was seen with Dr. Alfred Bielschowsky, who agreed that there was complete isolated congenital paralysis of the right inferior rectus muscle. He advised an advancement of the inferior rectus muscle with recession of the superior rectus muscle. The following day, after anesthetization with procaine hydrochloride, an operation to advance the inferior rectus muscle was started,

13. Hardy, W.: Congenital Anomalies of the Eyes, in Wood, C. A.: American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1914, vol. 4, p. 2800.

14. Coover, D. H., cited by Hardy.[13]

but careful investigation revealed no inferior rectus muscle. Preoperatively, total congenital paralysis cannot be differentiated from congenital absence of a muscle, so that the operator must be constantly on guard when operation is contemplated for congenital motor anomalies. Dr. Verhoeff came to the operating room, and it was also demonstrated to his satisfaction that there was no evidence of any inferior rectus muscle, not even a slight rudiment. The tendons of the medial, superior and lateral rectus muscles were located and appeared normal as to size, location and insertion. Dr. Verhoeff stated that in his years of experience as a pathologist and surgeon he "had never before seen the congenital absence of a muscle." I considered doing a Hummelsheim operation, of which I have done a few. Instead,

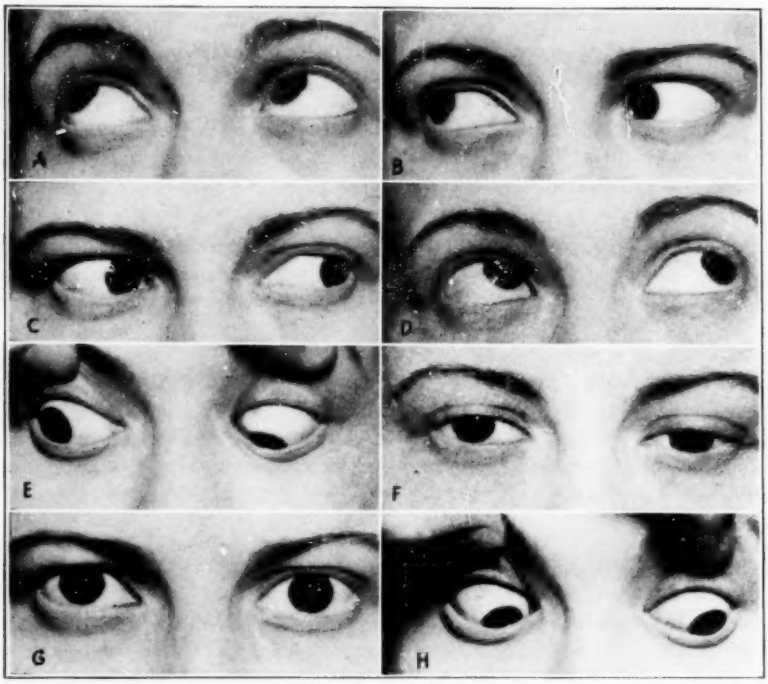

Fig. 1 (case 1).—*A* to *G*, preoperative views of patient made on April 13, 1938, showing the eyes in the various cardinal positions. The right eye became elevated when the patient looked to the right (*B*), but there was parallelism of the visual axes when she looked to the left (*C*). When she looked down and to the right, no action in the field of the right inferior rectus muscle could be demonstrated (paralysis or absence of the muscle [?]). The position of the eyes when fixing with the right eye is shown in *F* and the habitual position of the patient's eyes when fixing with the left eye in *G*.

I tenotomized and split the external rectus tendon, transplanting the lower half where the outer half of the inferior rectus muscle should have been and placing the upper half on its own lower border. I sutured them with 000 ten day chromic catgut after the sclera had been made rough. The conjunctiva was closed with fine silk sutures. A double eye patch was kept on for five days. There was

little postoperative reaction. Figure 2 shows the postoperative result on May 19, 1938. At this time the patient was thoroughly studied by Dr. Verhoeff,[15] who found a remarkably large field of binocular single vision, good fusional amplitude, little cyclophoria, normal convergence in the midline and excellent depth perception.

A recent letter from the patient indicates that she is very grateful. Her eyes are straight all the time, and there has been no upshoot since the operation. She can read for long periods without fatigue, and she is not troubled with diplopia.

CASE 2.—*History.*—Mr. W. F., aged 19, was referred to me in March 1939, by Dr. J. J. Regan, for reoperation for marked congenital left hypertropia.

The patient stated that his left eye turned up all his life and that he was unable to look down and to the left (fig. 3). He became an outpatient at the Cambridge City Hospital at the age of 3 years for treatment of congenital left hypertropia. He did not remember having had diplopia, vertigo, nausea or dizziness.

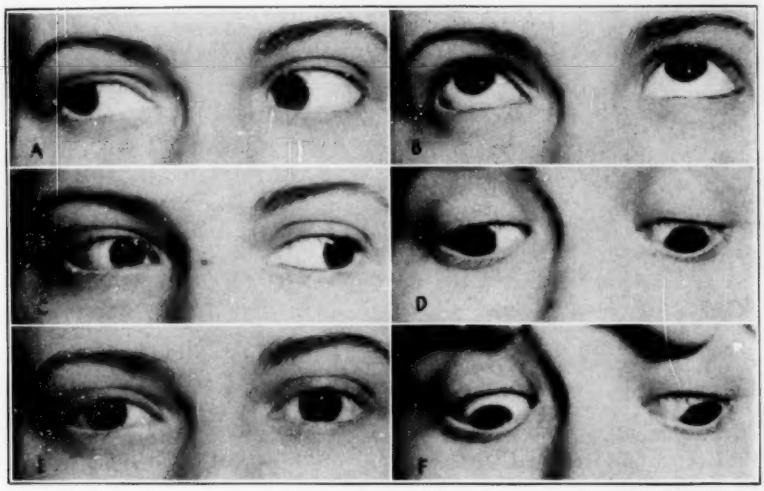

Fig. 2 (case 1).—*A* to *F*, postoperative views taken on May 19, 1938. In *A*, the eyes are rotated to the right, and the right eye shows only slight elevation. In *B* the patient is looking straight up. In *C* the eyes are to the left. Note that the operative field can still be seen in the right eye. In *D* the patient is looking down and to the right; there was a marked increased excursion of the right eye. In *E* the eyes are in the primary position. There were binocular single vision and good stereopsis. In *F* the eyes are down and to the left.

His general health had always been excellent. He had measles and mumps in childhood and had an operation for removal of tonsils and adenoids. The following ocular operations had been performed for left hypertropia: June 30, 1937, tenotomy of the right inferior rectus muscle, and Aug. 19, 1937, tenotomy of the left superior rectus muscle. On Nov. 27, 1937, the "conjunctiva was opened over the insertion of the left inferior rectus muscle, and congenital absence of the muscle was found. Consequently, the inferior third of the internal rectus was

15. Verhoeff, F. H.: Personal communication to the author.

separated for a distance of 1 cm. and sutured at a point on the sclera which would correspond to the outer margin of the insertion of the inferior rectus muscle."

There was nothing of significance in the family or social history.

Physical Examination.—The heart, lungs, abdomen and extremities were normal. The blood pressure was 125 systolic and 85 diastolic. General physical examination gave negative results except for abnormal findings limited to the left eye.

Ocular Examination.—Vision in the right eye was 20/20 with a +2.00 sph.; it was 20/40 in the left eye with a +3.00 sph. $\bigcirc$ —1.00 cyl., ax. 10.

In February 1939 the patient was first seen in the Bielschowsky-Casten postgraduate course on ocular muscles. The left eye deviated strongly upward at all times. The patient was unable to look down and to the left. In view of the preceding case, it was decided to reoperate and do the same operation but in addition to do a free tenotomy of the left inferior oblique muscle.

Fig. 3 (case 2).—Appearance of patient when 5 years old. The left eye shows marked congenital left hypertropia.

On March 11, with the left eye fixing, the right eye deviated downward 25 arc degrees; when the right eye fixed, the left eye deviated upward 25 arc degrees. There was also 10 to 15 degrees of convergence. There was no movement of the left eye down and out; no diplopia was noted unless the red glass was used. The patient showed both normal and anomalous retinal correspondence by the after-image test.

Except for the refractive error and muscular anomaly, the eyes were normal. The lids, cornea, anterior chamber, iris, pupils, lens, media and retina appeared normal.

On March 14, after anesthetization with procaine hydrochloride, the conjunctiva of the left eye in the lower, outer quadrant was freely incised. The external rectus muscle was tenotomized close to the globe and retracted so that the tendon of the inferior oblique muscle could be viewed. The latter was then freely and completely tenotomized. The transplant from the internal rectus muscle made at the third operation appeared small and fibrous. The external rectus muscle was then attached to the sclera, with 000 ten day chromic catgut, in a position corresponding to the outer border of the normally placed inferior rectus muscle and the

lower border of the former insertion of the external rectus tendon. The external rectus muscle was also advanced moderately during the transplantation. Convalescence was uneventful.

Two weeks later the eyes appeared on the same level; they maintained this level when rotated to the left. The postoperative result may be seen in figure 4. In September 1939 and January 1940 the patient showed 4 to 5 degrees of right hyperphoria in the primary position, which decreased to zero on looking slightly downward.

CONCLUSIONS

1. Isolated congenital absence of the inferior rectus muscle is rare.

2. Congenital paralysis of the inferior rectus muscle cannot be differentiated clinically from congenital absence of the muscle without operative investigation.

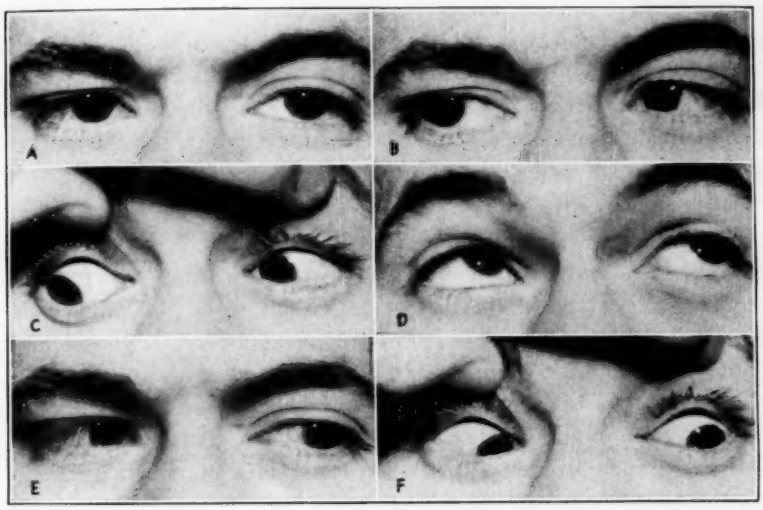

Fig. 4 (case 2).—In *A* the eyes are in the primary position; in *B*, to the right; in *C* down and right; in *D*, up and left; in *E*, left (horizontal) and in *F* down and left.

3. Congenital hypertropia resulting from absence of the inferior rectus muscle can be greatly improved by advancing and transplanting the external rectus muscle to a point midway between the normal position of the external and inferior rectus muscles.

4. If the hypertropia is excessive, tenotomy of the inferior oblique muscle should be combined with transplantation and advancement of the external rectus muscle.

5. The transplanted external rectus muscle then has two additional actions, extorsion and depression, both functions of the normal inferior rectus muscle.

INTRADIEM TENSION STUDIES IN CHRONIC SIMPLE GLAUCOMA

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The diagnosis of chronic simple glaucoma offers no difficult problem to the well trained ophthalmologist. For the progress of the disease, changes in the visual field furnish an accurate measure. For its control, there have been developed fairly effective medical and surgical measures. However, there remains the recurring problem of deciding on the wisest and most effective way of applying these measures to the individual case. Each time a new patient suffering from this disease presents himself, all the known factors in the case must be carefully evaluated and an attempt made to choose a course of treatment which for this particular patient seems the safest and most effective plan for preventing further loss of vision.

In deciding what course to follow, a number of factors must be considered. As far as the eye itself is concerned, first to be taken into account is the stage of the disease as evidenced by the central vision, the visual field and the ocular tension. Next are to be considered the depth of the anterior chamber and the condition of the filtration angle, the degree of transparency of the lens and the state of the vitreous and fundus. Then certain general factors, no less important, are to be considered, such as the patient's age, his state of general health and probable life expectancy, his temperament, his occupation and his cooperation in carrying out the treatment. When the patient has been examined from all these standpoints, one may still have insufficient data from which to plan the best campaign for checking the disease. Frequent determinations of the ocular tension may add considerably to these data and may early enable one to embark on the wisest course of treatment.

It has long been known that within the same day there may be marked variations in the ocular tension in glaucoma. Doubtless many ophthalmologists make a practice of studying these variations, but it seemed to me that the importance of the information to be gained in this way has not been sufficiently emphasized and that it would be worth while to record my results of such tests on a series of patients. Some years ago I began making such studies of the tension in occasional cases of chronic simple glaucoma, at first in a rather haphazard manner

and later after a more systematized plan. As the value of these studies became apparent, they were made on more and more patients. The patients chosen for the study were those in regard to whom the question of whether or not to operate was still in doubt, including particularly those with characteristic changes in the optic disk and visual field but whose tension taken at the usual intervals was always relatively low. In addition to these, some older patients with elevated tension on whom I was reluctant to operate were studied in order to determine the most effective nonsurgical treatment.

The plan usually followed was to hospitalize the patient and have a member of the house staff take the tension four times daily, approximately at 8 a. m., 12 noon, 6 p. m. and 10 p. m. A few readings were taken in the middle of the night, and a few patients who lived nearby came to the hospital four times daily. After one or more days without treatment, a miotic was prescribed and the study continued; in some instances it included the determination of the effect of different miotics or of different strengths of the same miotic. The total period of study was usually from three to five days. The miotic was usually changed daily.

No doubt a more valuable study would include readings of tension taken during the night. No doubt, also, with the patient in the hospital away from the stresses and strains of business and the home, the tension may be lower than if he were going about his daily activities. A longer period of study might show more accurately the effect of a miotic on the tension, since the full effect may not always be obtained until it has been used two or three days. The plan followed was chosen for its feasibility from the standpoint of the patient and the house staff.

The results in 22 cases are presented. The cases can be roughly divided into the following three groups, though the divisions are not always absolutely clearcut: (1) cases in which the tension was always well within the normal range without treatment and was little if at all affected by miotics; (2) cases in which the tension was sometimes elevated but was maintained at a normal level with some miotic and (3) cases in which the tension was sometimes elevated and was not satisfactorily controlled with any miotic used.

In group 1 there are 7 cases (charts 1 to 7). In spite of the relatively low tension all patients showed cupping of the disk of the glaucomatous type and changes in the visual field of a sort characteristically seen in cases of glaucoma. I am aware that some ophthalmologists would not classify these as cases of glaucoma. If they are not so classified, however, there is nothing to offer the patients in the way of treatment. If they are accepted as true cases of glaucoma, how can the consistently

low tension be reconciled with such a diagnosis? Three possible explanations which may be offered are:

1. The normal tension for such eyes is lower, possibly 8 to 10,[1] and a tension of 18 to 25 represents for these eyes a true glaucomatous elevation.

2. The normal tension for these eyes is 18 to 25, but there may be periodic rises in tension during which damage is done to the eye.

3. There has been a true glaucomatous state in the eye in the past, which has been spontaneously arrested.

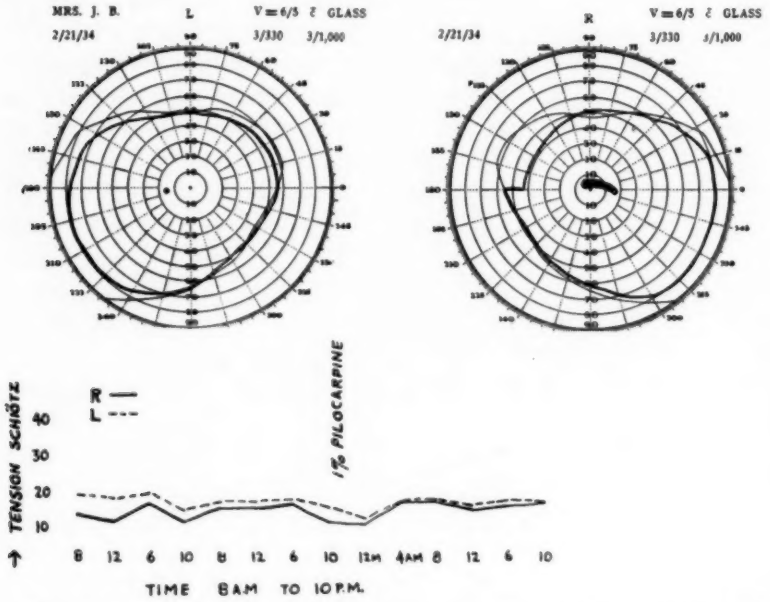

Chart 1.—Visual fields and tension curves of Mrs. J. B., aged 44. Definite loss of field occurred in the right eye over a period of six months in spite of the faithful use of a miotic. Trephining was done. Tension was maintained under 12 for the next four years with no further loss of field. Six months later further loss was discovered. It was then found that the filtering scar had partially closed and that tension was 20. The left eye still shows no evidence of glaucoma after six years. (To save space all fields shown represent a composite of the fields at 330 cm. and at 1 meter.)

That the first explanation may sometimes be the true one is suggested by an analysis of cases 1, 2 and 4. In case 1, although the patient used a miotic faithfully, over a period of observation of several months there was an increase in the cupping of the disk and definite loss of

1. All tensions herein given were recorded with the new Schiötz tonometer.

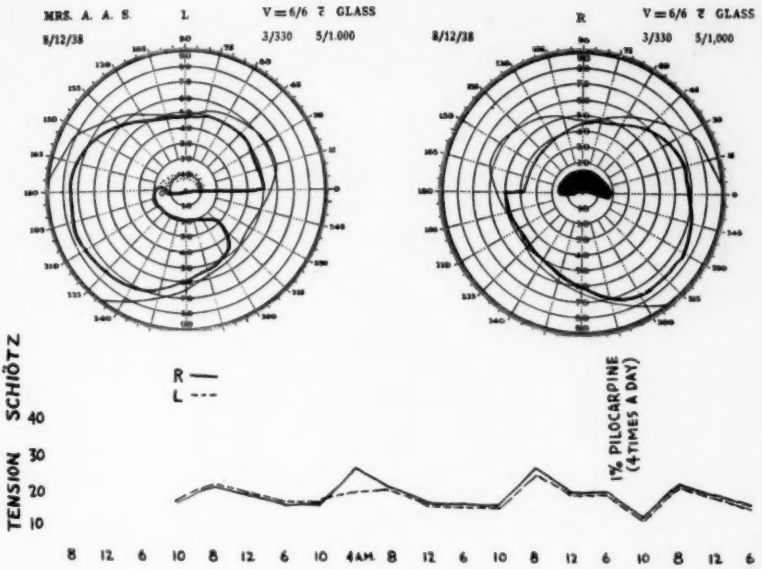

Chart 2.—Visual fields and tension curves of Mrs. A. A. S., aged 57. Loss of field occurred in the left eye over a six month period in spite of the faithful use of a miotic. Trephining was done. Tension has been maintained under 12 since the operation. No further loss of field occurred in one year. There was slight loss of field in the right eye. Operation is contemplated on this eye.

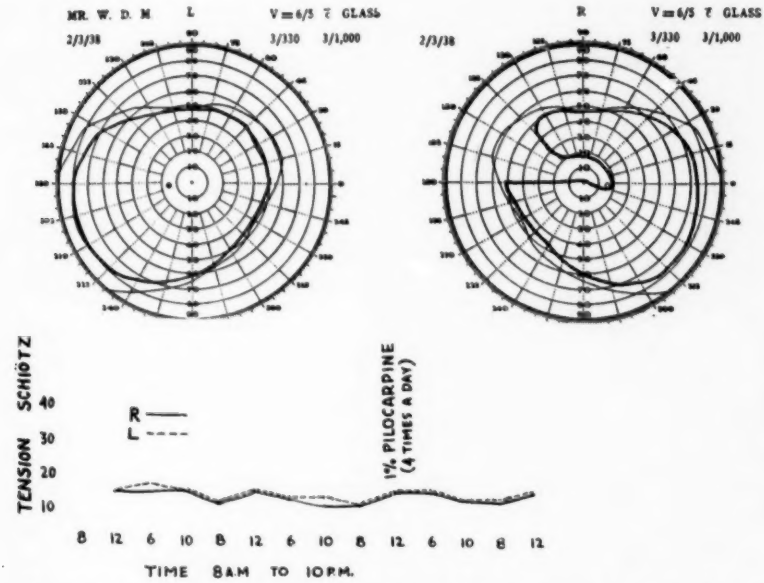

Chart 3.—Visual fields and tension curves of Mr. W. D. M., aged 61, who has been under observation for over one year. He has faithfully used a miotic. Tension has never been found higher than 19. No loss of field has taken place.

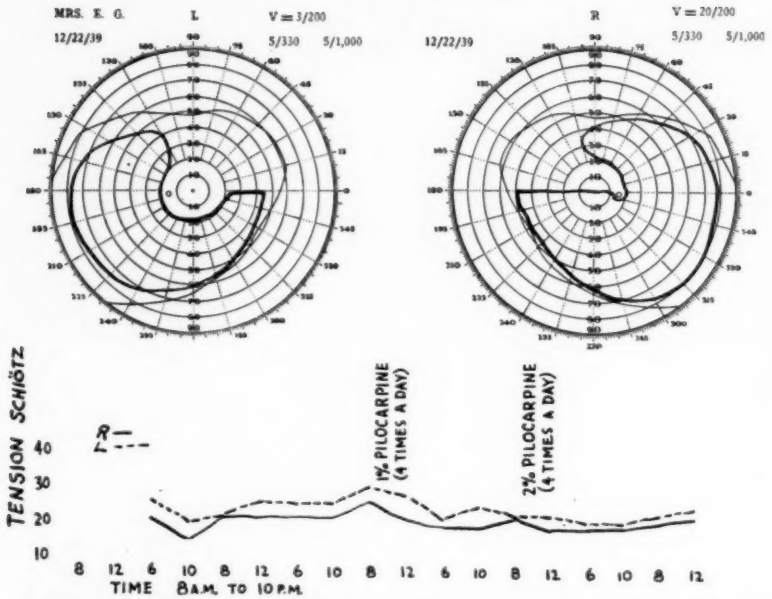

Chart 4.—Visual fields and tension curves of Mrs. E. G., aged 68. There were marked cupping of the disk and exfoliation of the lens capsules. Since there was no substantial lowering of tension with miotics, further loss of field was to be expected, and both eyes were operated on.

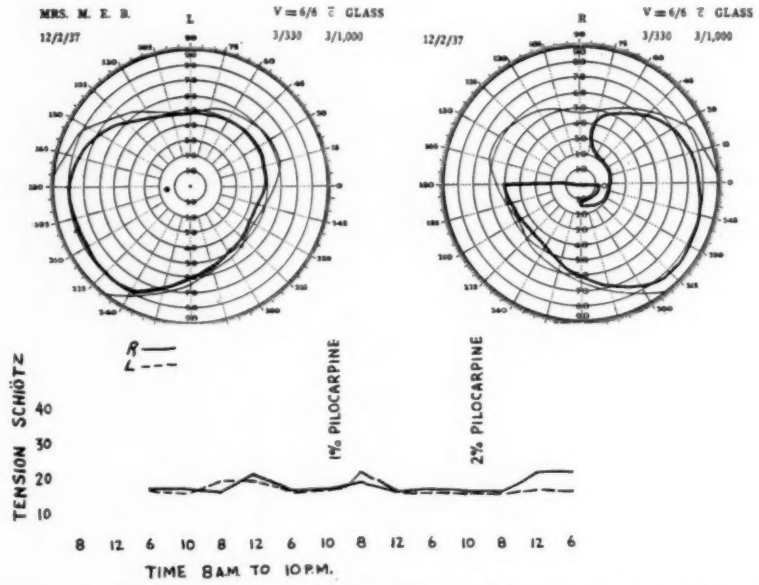

Chart 5.—Visual fields and tension curves of Mrs. M. E. B., aged 68, who has been under observation for two years. She has used a miotic faithfully. She has heart disease and leads a restricted life. Tension has never been found higher than 19. There has been no further loss of field.

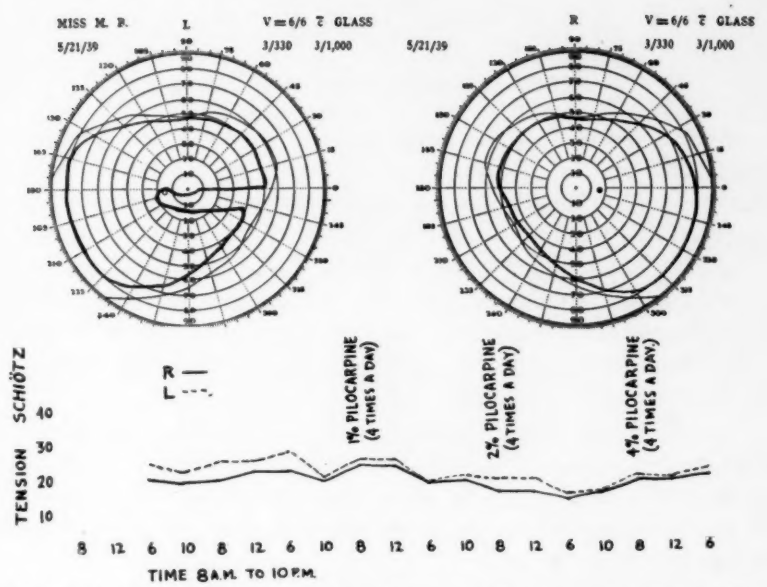

Chart 6.—Visual fields and tension curves of Miss M. B., aged 60, who has been under observation for eight months. She has used miotics faithfully. There has been no further loss of field.

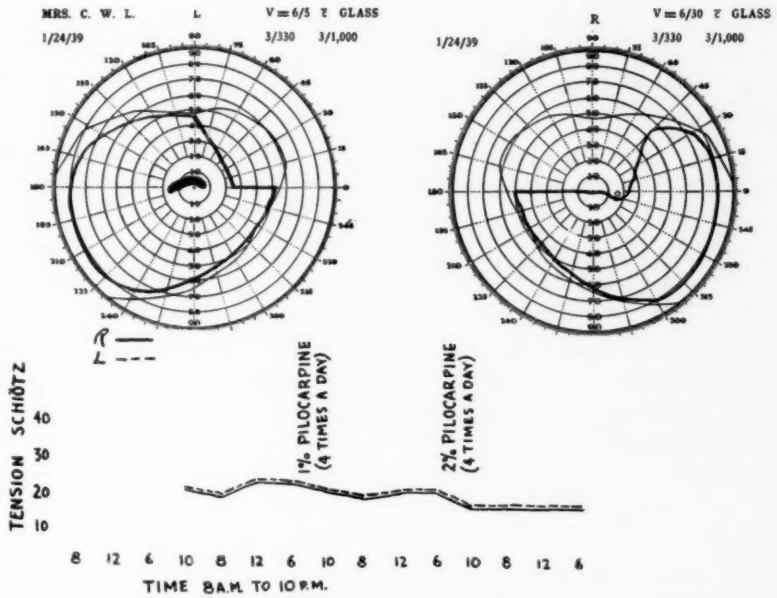

Chart 7.—Visual fields and tension curves of Mrs. C. W. L., aged 75. She was under observation nine years prior to the tension studies. When she was first seen the field of the left eye was normal and the field of the right eye was much larger than pictured here. Loss of field apparently was not gradual but in steps. Sometimes for a period of a year no loss of field could be demonstrated. A few months later further loss would be found. Tension was never found higher than 22 in either eye except on one occasion, when tension of 35 was found in the right eye. A miotic was not used faithfully. A hole in the macula of the right eye accounts for the low central vision. Operation has been advised but not accepted.

visual field. Trephining was done, and tension was subsequently maintained at 12 or less. During the next four years there was no loss of visual field. Six months later a further loss of field was noted, and it was found that the filtering scar had partially closed and tension was 20.

In case 2 the patient likewise suffered from loss of visual field in the left eye while under observation. Trephining was done, reducing the tension to 12 or less. One year after operation the field in this eye is unchanged. The right eye has shown slow loss of field, and operation on this eye is contemplated.

In case 4 there were marked cupping of the disks and exfoliation of the lens capsules. It was felt that the tension recorded represented a true glaucomatous state for these eyes, and since miotics apparently had no appreciable effect, operation was performed on both eyes without further observation.

In case 7 the second explanation may possibly apply. The patient has been observed for nine years. During this time for periods of as much as a year at a time no loss of visual field was discoverable in either eye. Then at later visits further losses would be found to have taken place. On one occasion a tension of 35 was found in the right eye, but at no other time was it ever found over 22 in either eye. Miotics have never been used consistently. The apparently periodic loss of visual field may have been caused by periodic elevation of tension.

In the other 3 cases in this group the third explanation may apply. No further demonstrable loss of visual field has occurred, but the patients have not been observed for a long time. A longer period of observation may provide the answer to this problem. It is my feeling that miotics are of no value in this group of cases and that if loss of field continues surgical intervention must be considered.

In group 2 (charts 8 to 16) it can be seen that for the most part tension was maintained with the use of some miotic at what would seem to be a satisfactory level for those eyes. In this group it would appear that a miotic can be employed with reasonable assurance that the disease will be held in check. Possibly later the tension may not be so well controlled, and the plan of treatment may have to be revised. In case 16, however, there was not the slightest additional loss of visual field during a period of observation of nearly six years. None of the patients in this group has been operated on to date, except the patient in case 10. In this case there was marked exfoliation of the lens capsule, and tension was relatively high and unaffected by the use of ordinary miotics. The right eye was already blind from glaucoma. Although in the left eye the tension was controlled by the use of stronger miotics while the patient was being studied in the hospital, at subsequent visits

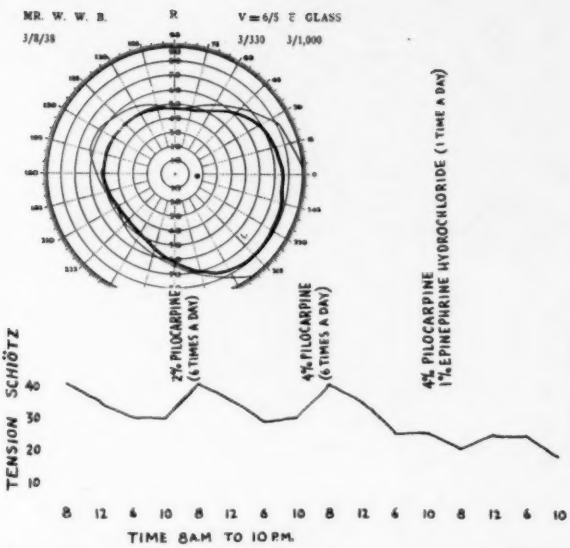
MR. W. W. B.
3/8/38
R
V=6/5 ē GLASS
3/330 3/1,000
2% PILOCARPINE (6 TIMES A DAY)
4% PILOCARPINE (6 TIMES A DAY)
4% PILOCARPINE 1% EPINEPHRINE HYDROCHLORIDE (1 TIME A DAY)
TENSION SCHIÖTZ
40
30
20
10
8 12 6 10 8 12 6 10 8 12 6 10 8 12 6 10
TIME 8 A.M. TO 10 P.M.

Chart 8.—Visual field and tension curve of Mr. W. W. B., aged 64. The left eye was trephined in 1926 for advanced glaucoma and enucleated a few months later for panophthalmitis. Tension of the right eye was first found elevated in 1938. Tension was unaffected by the use of pilocarpine alone but was controlled when a 1 per cent solution of epinephrine hydrochloride was used once a day in addition to the miotic. Two later studies of one day each have been done. Tension was always found to be normal. There has been no loss of field up to the present time.

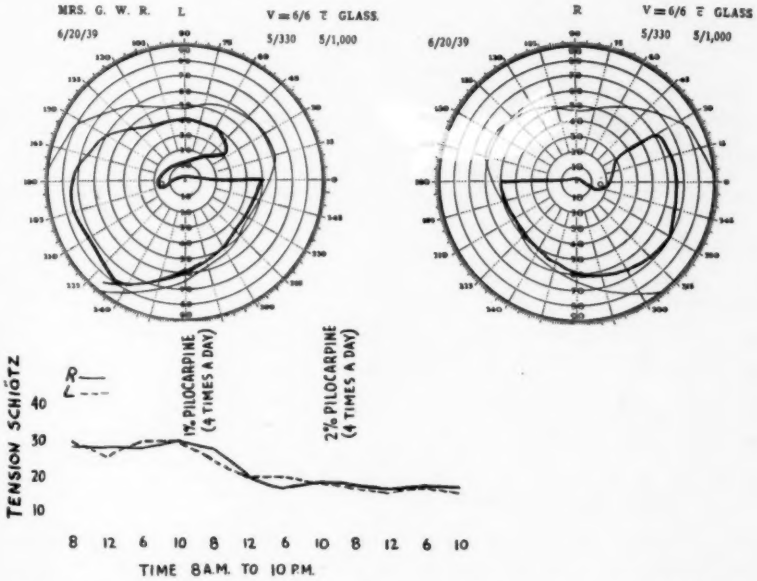

Chart 9.—Visual fields and tension curves of Mrs. G. W. R., aged 73. Tension is apparently well controlled with the use of a miotic.

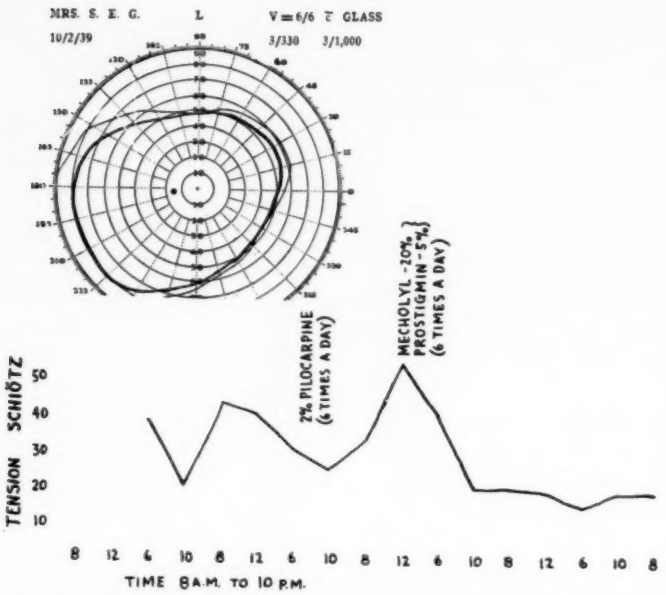

Chart 10.—Visual field and tension curve of Mrs. S. E. G., aged 69. There were absolute glaucoma in the right eye and exfoliation of the lens capsule in both eyes. Relatively high tension was controlled only with the use of the strongest miotics. The patient was discharged without operation. At subsequent visits to the office tension again was found elevated, and operation was done on the left eye.

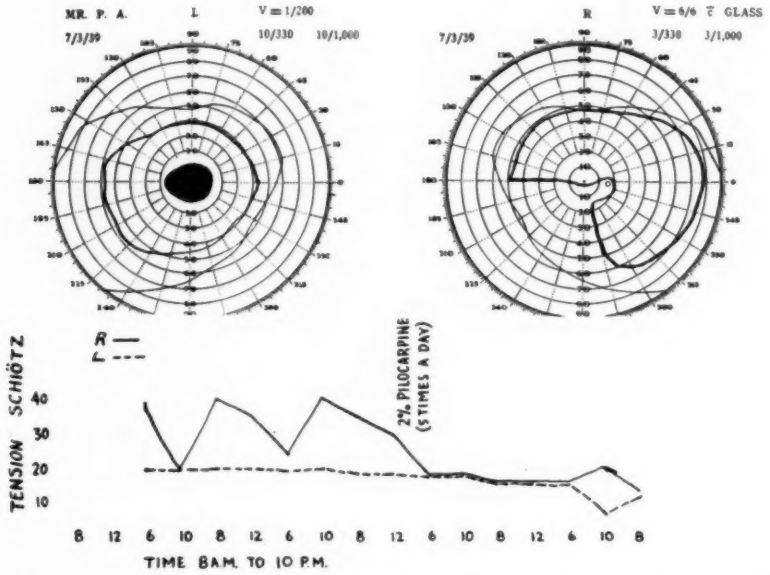

Chart 11.—Visual fields and tension curves of Mr. P. A., aged 62. The patient was seen because of sudden loss of vision in the left eye. Occlusion of the central retinal vein was found in this eye and chronic simple glaucoma in the right eye. The tension is apparently well controlled with the use of a miotic.

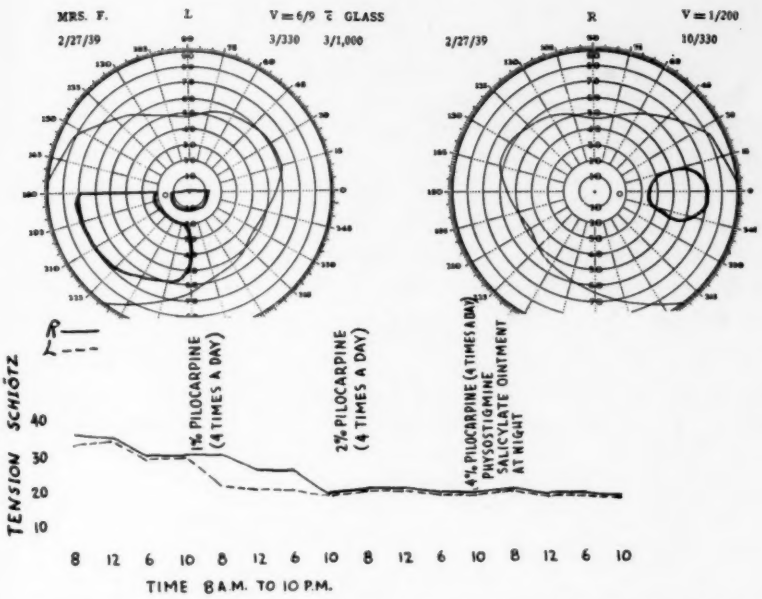

Chart 12.—Visual fields and tension curves of Mrs. F., aged 67, with advanced glaucoma. The tension is apparently controlled with the use of a 2 per cent solution of pilocarpine. Operation is not contemplated for the present.

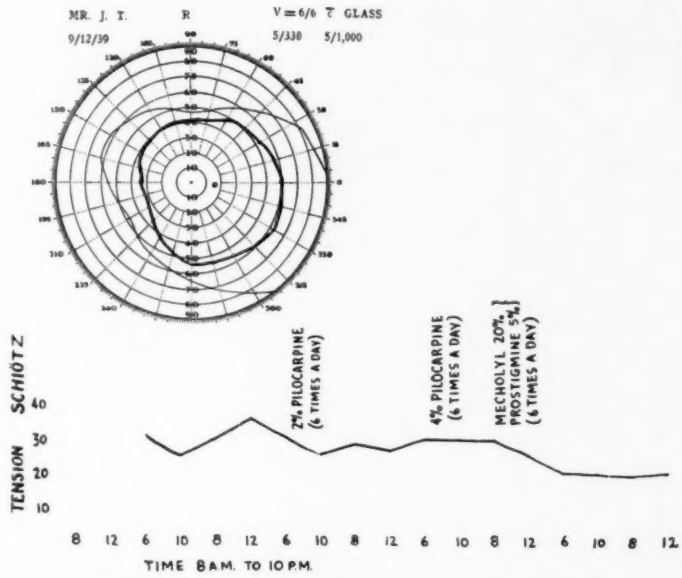

Chart 13.—Visual field and tension curve of Mr. J. T., aged 64. He had a history of acute glaucoma in both eyes two months before these data were recorded, with enucleation of the left eye and trephining of the right eye. He now shows no evidence of filtration. The disk is atrophic but not cupped. The tension is apparently controlled with the use of strong miotics. There is a strong probability that operation will be required eventually.

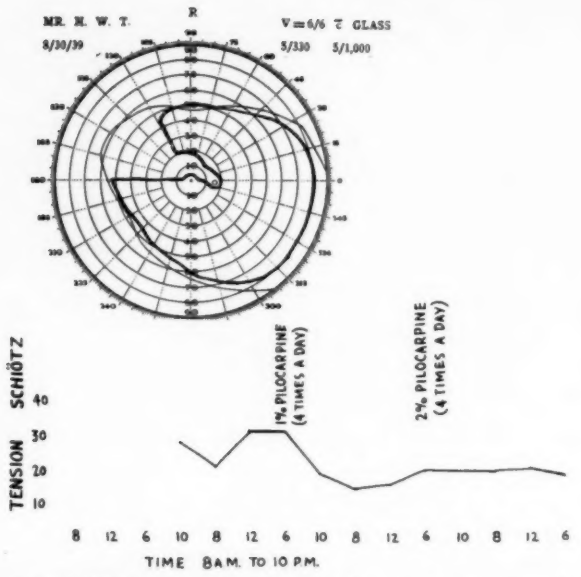

Chart 14.—Visual field and tension curve of Mr. H. W. T., aged 61. The left eye shows absolute glaucoma. Tension in the right eye is apparently controlled with the use of a 2 per cent solution of pilocarpine. Operation is not contemplated for the present.

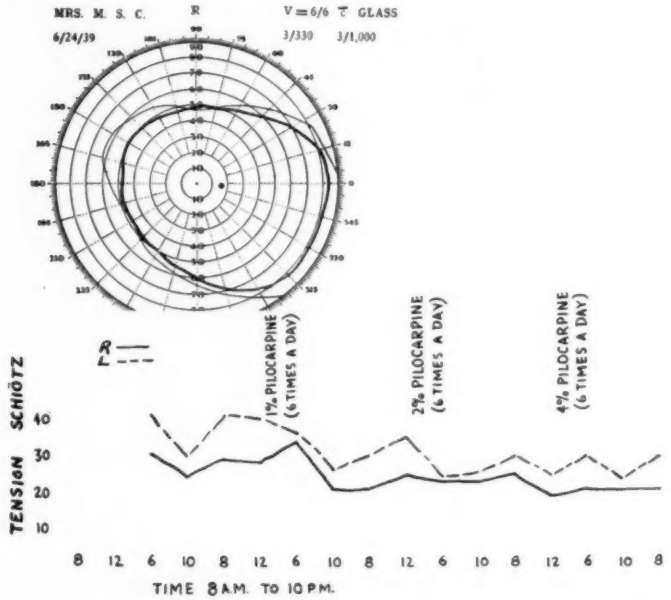

Chart 15.—Visual field and tension curves of Mrs. M. S. C., aged 71. There is absolute glaucoma of the left eye. Tension in the right eye is apparently satisfactorily controlled with the use of a 4 per cent solution of pilocarpine. Operation is not contemplated for the present.

to the office the tension was found considerably elevated. Treatment with miotics was regarded as unsafe, and although the field was still normal operation was performed on this eye.

I have had similar experience in other cases in which during the short periods the tension was studied strong miotics were required to maintain the tension in the normal range. In most of these patients the tension was later found again elevated. In such cases I believe that operation is indicated.

In group 3 (charts 17 to 22) it can be seen that no substantial lowering of the tension was obtained with the use of miotics during the

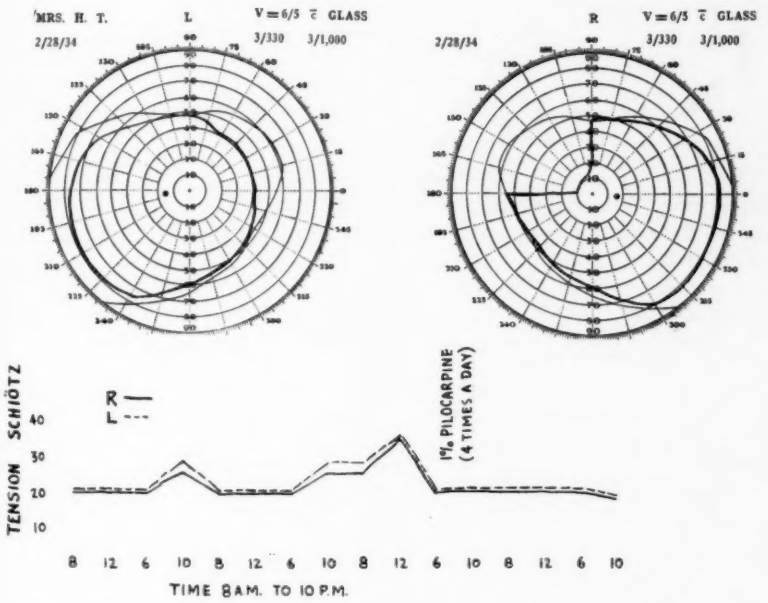

Chart 16.—Visual fields and tension curves of Mrs. H. T., aged 61. Periodic rises in tension apparently are prevented by the use of a 1 per cent solution of pilocarpine. The patient has been under observation nearly six years since this study was made. Miotics have been used faithfully, and there has been no further loss of field.

period of special study of the tension. It must be concluded that operation is necessary in these cases if the disease is to be controlled. All of these patients have had an operation except the patients in cases 17 and 18. The patient in case 17 was an 85 year old woman with heart disease, and in this case the studies were undertaken to determine the most effective miotic. In case 18 there has been little loss of visual field in two years. It will be seen that the tension curve tended to flatten out

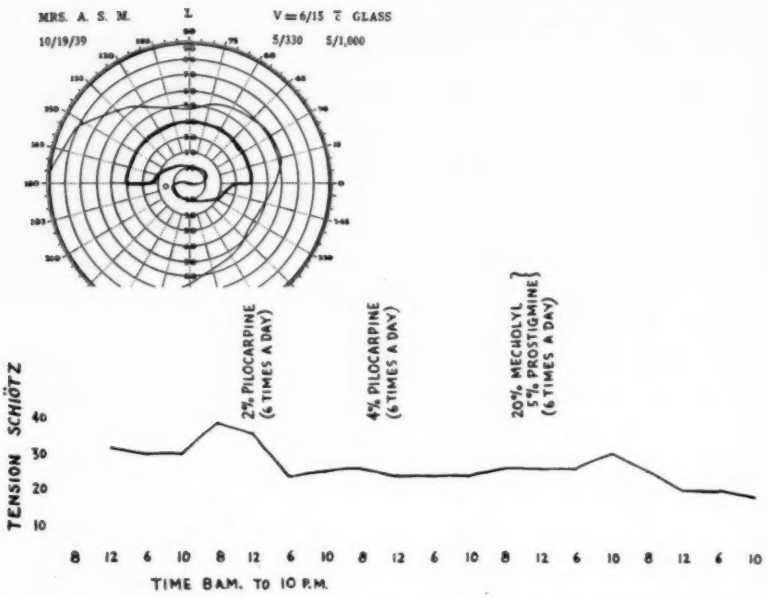
MRS. A. S. M.
10/19/39
L
V=6/15 T GLASS
5/330 5/1,000
2% PILOCARPINE (6 TIMES A DAY)
4% PILOCARPINE (6 TIMES A DAY)
20% MECHOLYL 5% PROSTIGMINE (6 TIMES A DAY)
TENSION SCHIÖTZ
40
30
20
10
8 12 6 10 8 12 6 10 8 12 6 10 8 12 6 10 8 12 6 10
TIME 8 A.M. TO 10 P.M.

Chart 17.—Visual field and tension curve of Mrs. A. S. M., aged 84, with heart disease. The right eye shows absolute glaucoma. Tension studies were made to discover the most effective miotic for the left eye. Operation is not contemplated.

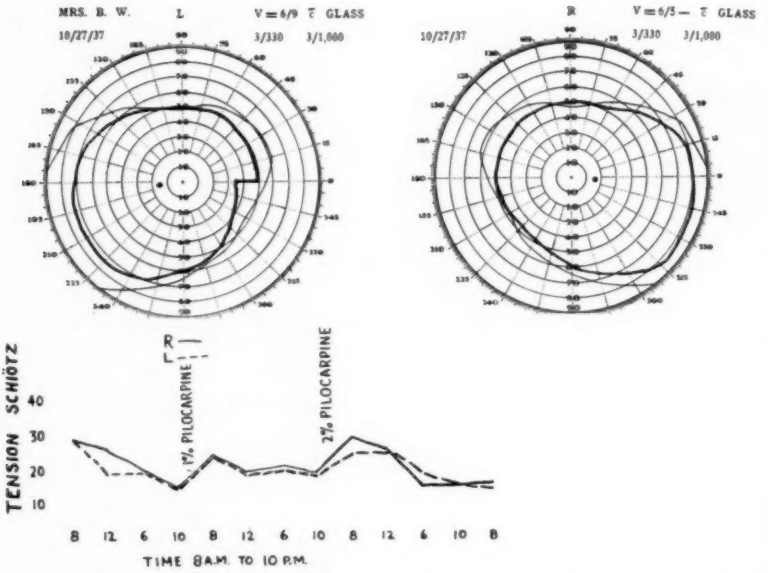

Chart 18.—Visual fields and tension curves of Mrs. B. W., aged 65, with incipient cataract in the left eye. The patient has been under observation for two years. A 2 per cent solution of pilocarpine has been used faithfully. Tension has never been found higher than 25. There has been only slight loss of field. Operation is not contemplated at present.

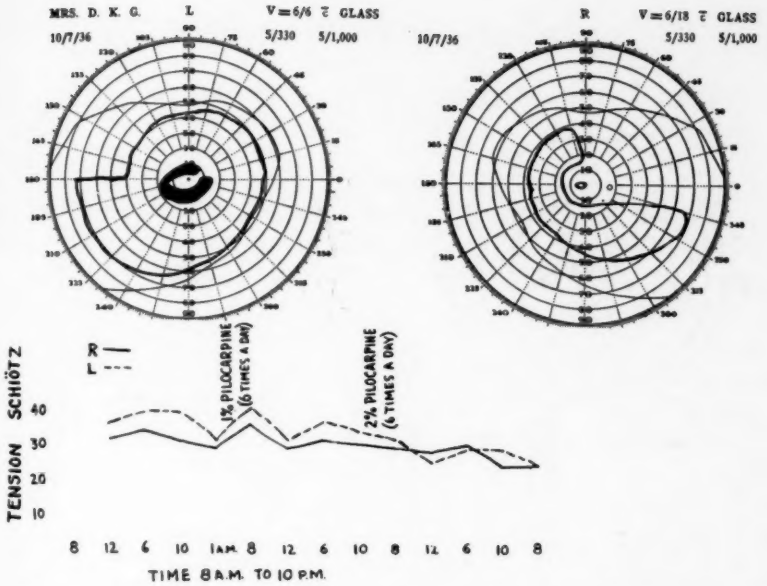

Chart 19.—Visual fields and tension curves of Mrs. D. K. G., aged 66. There were atypical cupping of the disks and unusual visual field changes. There was definite loss of field in both eyes in a year. Trephination was done on both eyes in 1937. Tension was under 12 thereafter, and no further loss of field has taken place.

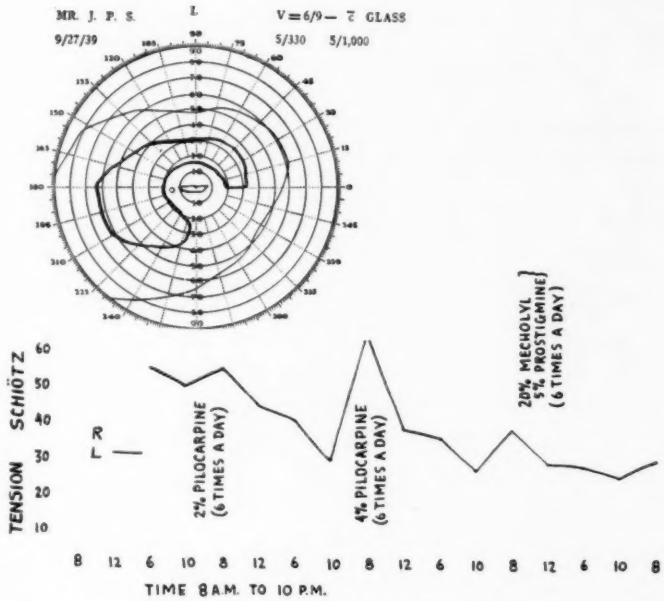

Chart 20.—Visual field and tension curve of Mr. J. P. S., aged 68. The right eye showed absolute glaucoma. In the left eye relatively high tension was maintained only at a level of 30 with strong miotics. Operation was done without delay.

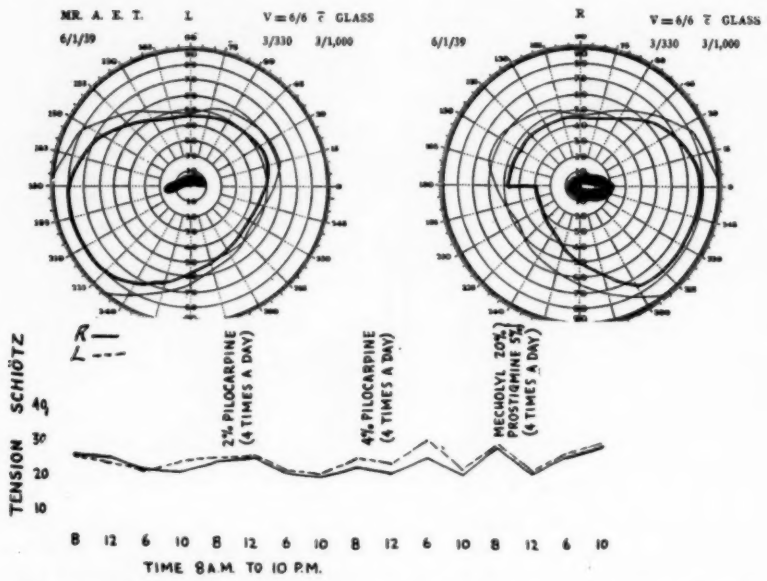

Chart 21.—Visual fields and tension curves of Mr. A. E. T., aged 62. Miotics had no significant effect on tension. Operation was done on both eyes.

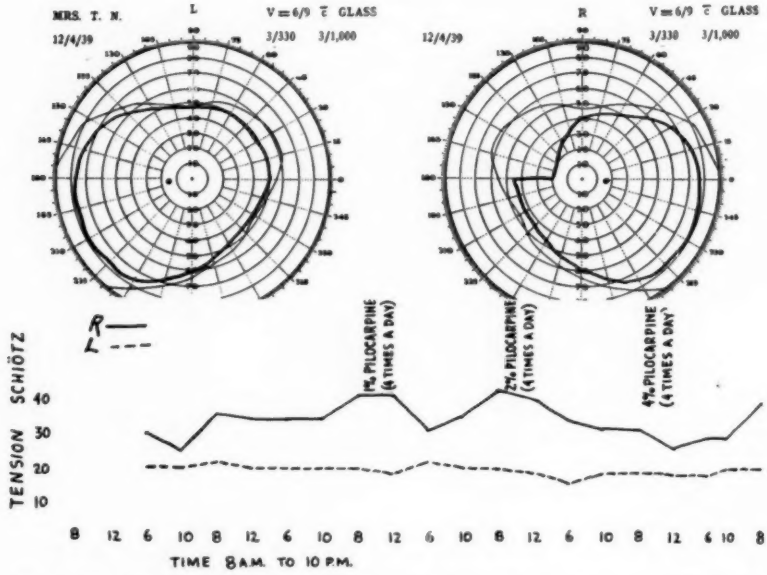

Chart 22.—Visual fields and tension curves of Mrs. T. N., aged 69. The left eye is normal, and there was early glaucoma in the right eye. Miotics had no significant effect on the tension. Operation was done on the right eye.

toward the end of the study, and at subsequent visits to the office tension has been found to be well controlled. This case may well belong in group 2.

The foregoing studies confirm the fact that there are many cases of chronic glaucoma in which marked intradiem variations in tension occur. This is true of several of the cases in the present series. Tension readings taken at the usual intervals might fail to reveal these periodic rises, so that loss of field might be the first indication that the treatment was ineffective. It would be advantageous to make such studies in all cases of chronic glaucoma, since they would indicate at the outset the best form of treatment to be employed. However, for the purpose of deciding the question of operation, in my opinion such studies are unnecessary for the following patients:

1. Relatively young patients. For these it is my usual practice to advise operation, irrespective of the tension and the immediate effect of miotics. I feel that early operation is always preferable to late and that few patients with chronic glaucoma who have a probable life expectancy of twenty or thirty years can be expected to maintain their vision satisfactorily by miotic treatment alone.

2. Most older patients whose tension always or at times is found to be high in spite of ordinary treatment with miotics. For these patients I usually advise operation without further investigation, unless it is contraindicated by the advanced age of the patient or serious constitutional disease.

SUMMARY AND CONCLUSIONS

Twenty-two cases of chronic simple glaucoma are reported in which intradiem tension studies were done. The tension was taken four times daily, approximately at 8 a. m., 12 noon, 6 p. m. and 10 p. m. The period of study was from three to five days. The first day of the study no treatment was employed. On the succeeding days different miotics were used, and their effect on the tension was recorded. In the first group of patients the tension was always found to be within normal limits and was little, if at all, affected by miotics. In the second group the tension was sometimes found to be elevated but was maintained at normal levels with some miotic. In the third group the tension was sometimes found to be elevated and was not satisfactorily controlled by miotics.

In some cases the studies furnished valuable data for deciding whether or not to operate. When operation was contraindicated for general reasons, the study helped to determine the most effective miotic therapy.

WALTZING GUINEA PIGS WITH PARTICULAR REFERENCE TO OCULAR MOVEMENTS AND RIGHTING REFLEXES

DAVID G. COGAN, M.D.
CAMBRIDGE, MASS.

I became interested in the ocular movements of waltzing guinea pigs about two years ago when, by chance, I observed that they did not show the normal vestibular nystagmus on being rotated. I called this to the attention of Dr. Lurie whose guinea pigs they were and who has since reported [1] this phenomenon along with some observations of his own. But as the methods which I employed for eliciting this phenomenon have not been described and as I have made several additional observations on waltzing guinea pigs, it is my purpose in this paper to discuss the subject more fully. The importance of these observations rests on the fact that they contribute, to some extent at least, to the meager knowledge of the vestibulo-oculomotor relation.

Waltzing, or circling, guinea pigs are not unlike the famous dancing mice. When excited, instead of running along the edge of the cage they make characteristic circling movements, which for any one guinea pig are predominantly in one direction. When not excited, such an animal generally stands with head tilted to one side and may show peculiar nodding or acquiescent movements of its head. It is impossible to say whether these characteristic movements of the head are voluntary and serve some function (parallax?) or are merely ataxic movements. Waltzing is ordinarily a hereditary anomaly, and pure strains of waltzers may be bred, but as yet its hereditary type has not been worked out. Recently Lurie and Dempsey [1] claimed to have duplicated the condition by producing lesions in the interpeduncular nuclei. It is their belief that the defect in the hereditary waltzers must be in this region, although no pathologic lesion has as yet been identified. The vestibular apparatus, the vestibular nerve and its endings in the medulla are, according to the authors, histologically normal.

My observations can be recorded best in the order in which I made them.

From the Howe Laboratory of Ophthalmology, Harvard University, and the Massachusetts Eye and Ear Infirmary.

1. Lurie, M. H., and Dempsey, E. D.: Experimentally Induced Circling (Waltzing) in the Guinea Pig, Laryngoscope **49**:565 (July) 1939.

Normal guinea pigs, like most other mammals, show a characteristic nystagmus on being rotated. This is elicited, most simply, by holding the animal in one's arms and rotating with the animal back and fourth through 180 degrees or so. The nystagmus is regular and constant, with the fast component toward the side of rotation of the animal. That it is a true vestibular nystagmus and not of the optokinetic type is suggested by the fact that it is present in animals lacking optokinetic nystagmus, as in the rabbit, and in thalamic and midbrain guinea pigs.[2] Although to my knowledge this nystagmus on rotation is present in all normal guinea pigs, I have never found the slightest trace of it on examining 12 waltzers. With the possible exception of bilabyrinthectomized animals, this absence of rotatory nystagmus seems to be a pathognomonic sign of a waltzer and may serve to differentiate waltzing

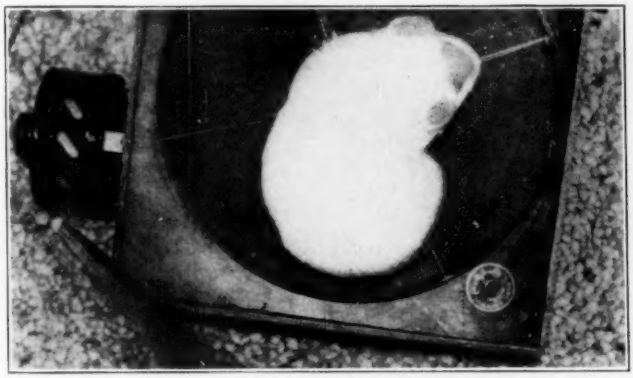

Fig. 1.—A normal guinea pig showing the characteristic posture assumed during rotation of the drum, the drum being rotated counterclockwise at the rate of one revolution per second.

from normal guinea pigs within a few days after birth, even before definite circling movements have been observed.

A somewhat more elaborate study of this nystagmus on rotation was made by utilizing an old electric victrola base, suitably modified so that its disk could be rotated at different speeds and in each direction. When guinea pigs were placed on the rotating disk, nystagmus occurred regularly in the normal guinea pig but was invariably absent in the waltzer. If the rotation was fairly rapid, two revolutions per second, and then suddenly stopped, the normal guinea pig showed a postrotatory nystagmus lasting ten to twenty seconds with the fast component toward the side opposite that of the previous rotation. None of the waltzing guinea pigs showed the slightest indication of postrotatory nystagmus.

2. Pestellini, G.: Effect of Repeated Rotation on Ocular Nystagmus with Intact Guinea Pigs and Thalamic Animals, Boll. Soc. ital. di biol. sper. **12**:393, 1937; abstracted, Zentralbl. f. d. ges. Augenh. **40**:173, 1938.

Quite similar to the ocular nystagmus, there was in the normal guinea pig a rhythmic oscillation of the head during rotation and immediately following it. This might be called head nystagmus, as it consisted of a fast and slow component similar to that of the ocular movements. During rotation the fast component was to the side toward which the animal was being rotated, while in the postrotatory phase it was to the opposite side. The waltzing guinea pigs showed no suggestion of head nystagmus either during the rotation or following it.

A further point of difference between these waltzers and normal guinea pigs was evident in the body position which they assumed during rotation as well as in their activity during and following the rotation. While being rotated, the normal guinea pig turned his head and shoulders to the side opposite that of rotation, so that he assumed a curled up

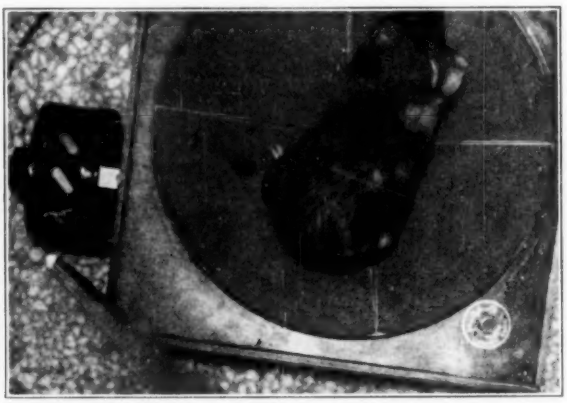

Fig. 2.—A waltzing guinea pig. No unusual posture is assumed despite rotation of the drum at the same rate as for the guinea pig in figure 1.

position, with nose apposed to hindleg and back convex toward the side of rotation. Aside from nystagmus of head and eyes, a normal guinea pig showed no movement during the rotation except perhaps a few extensor gestures of the limbs on the convex side of the body. The normal guinea pig appeared frightened and distinctly uncomfortable during this rotation and for several minutes thereafter. The waltzer, however, showed no tendency during the rotation to curl up. He maintained the same position as though he were not being rotated. He either remained stationary or made the same nodding movement of his head and irregular movements of his head and body which he made when in the stationary cage. Neither during the rotation nor subsequently did he seem upset or frightened, as does the normal guinea pig.

In view of the foregoing differences found between the normal and the waltzing guinea pig on rotation, I next compared their responses

with the Bárány test. This is an easy and satisfactory test on the guinea pig. First I irrigated the auditory canals of normal guinea pigs with ice water and found that a lasting nystagmus could be regularly produced within a few minutes after the irrigation was begun. But ice water was without any effect on the ocular movements of waltzing guinea pigs even with prolonged irrigation.

One other observation of interest is that in contradistinction to the normal guinea pig the waltzer shows no compensatory ocular movements or skew deviations when the head is tilted to one side. The previous observations have been concerned chiefly with the semicircular canal (ocular muscle complex or the statokinetic reflexes), but the absence of skew deviation is concerned with the utriculosacculus (ocular muscle complex, the mediator of static reflexes of the eyes). With the static, like the statokinetic reflexes, there was a characteristic absence of ocular responses.

Whatever the cause of the waltzing might be, it was apparent that there was in these animals a typical absence of functional coordination between the labyrinth and the ocular muscles. Yet the connections between the motor nuclei and the ocular muscles were intact, for the guinea pigs did show ocular movements (voluntary?) indistinguishable from the normal when struggling to get away. Also the pupils of these waltzing guinea pigs were of normal size and showed normal reactions.

After I had established beyond any doubt that absence of the response of the eyes and head to vestibular stimulation was characteristic of the waltzing guinea pig, it occurred to me that the failure of compensatory ocular movements might be the cause of the waltzing. This, however, I found not to be so, for removing the eyes from a waltzer did not prevent waltzing, while removing the eyes from a normal guinea pig did not produce waltzing.

This led me further to investigate the righting reflexes, and to my surprise [3] I found them distinctly and characteristically abnormal in the waltzing guinea pig. When a waltzer is turned over on the table, he will promptly right himself in a way not grossly different from the normal. If, however, the animal is turned over in the hand, he will show less resistance to the turning and will remain upside down more tranquilly than will the normal guinea pig.

More striking still is the following observation: If a normal guinea pig is dropped from a height of 1 to 2 feet (33 to 60 cm.) and allowed to fall on a blanket, he will land on his four feet, as in the familiar case of the cat. If the normal guinea pig is turned upside down and allowed to fall, he will right himself in midair quite as efficiently as will the cat.

3. I was surprised because the only reference in the literature heretofore states that the righting reflexes in the waltzing guinea pig are normal (footnote 1).

And what is more, blindfolding will not in the least impair his ability to right himself in midair. The situation with the waltzing guinea pig is quite different. The waltzer will attempt to right himself in midair, but in contrast to the normal guinea pig, he does it much less effectively and only rarely does he land squarely on his four feet. Nevertheless, one must admit there is an attempted but generally unsuccessful righting in midair. Most striking, however, is the observation on the falling waltzer when he is blindfolded. In this case the animal falls without making any attempt to right himself. He lands squarely on his back in exactly the same position in which he was dropped. After landing, however, and when contact is made with the ground, he quickly assumes the upright position.

Another experiment which I have contemplated but not undertaken is the immersion of a blinded waltzer in water. It is logical to predict that when the body is completely covered with water the animal will fail to show the normal righting reflex and drown more readily than will the normal blinded guinea pig.

Literature on the waltzing guinea pig is extremely scanty. Except for the one article cited here,[1] I have been unable to find references to the subject in the Index Catalogue of the Library of the Surgeon General's Office, in the Quarterly Cumulative Index Medicus or in Biological Abstracts.

CONCLUSIONS

1. Waltzing guinea pigs show a characteristic and complete absence of labyrinthine control over ocular movements and positions of the eyes, over movements of the head and positions of the head and over the righting reflexes.

2. Although labyrinthine control is absent in the waltzing guinea pig, the righting reflex is carried on with more or less success by the visual sense and by contact with the ground. These two criteria can be separately studied by allowing the animal to fall through the air with and without a blindfold and land on a flat surface. The righting in the air is for the waltzer a function of vision; the righting on a flat surface is in the case of the blindfolded waltzer a function of contact.

TUMOR OF THE LACRIMAL CARUNCLE

A STUDY OF TWO HUNDRED COLLECTED CASES

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Although tumors of the lacrimal caruncle are rare and hence do not present a major problem in ophthalmology, the individual case as it is encountered in practice may be perplexing and a cause of concern. If the oculist consults the standard textbooks on ophthalmology [1] he finds that they furnish little or no information of practical value. A good many individual case reports of various types of tumor of the lacrimal caruncle have appeared in the medical literature, but as yet these do not furnish any lucid criteria for classification of neoplasms in this region. And if the ophthalmologist turns to the pathologists for guidance in a particular case, he may be even more bewildered as to the type of tumor with which he has to deal.

When a case of tumor of the lacrimal caruncle was being studied a few years ago, these frustrating obstacles arose to obscure the formulation of a definite opinion. Of the diagnoses submitted by five pathologists, only two were in agreement that the tumor was a malignant melanoma of the mixed type. Another authority said that it was a nevus which could be called malignant only if the tumor should recur. A fourth diagnosis was adenocarcinoma of the gland of Harder, and still another, malignant embryoma containing undifferentiated sebaceous and sweat gland elements, neuronevus and melanotic components (figs. 1, 2 and 3).

Because of this experience, I addressed an inquiry to leading ophthalmologists and hospitals in the United States with the hope that a mass of material might be accumulated that would contribute something of value to the knowledge of this condition. Questionnaires or letters were sent to 1,700 physicians and hospitals, and approximately 325 replies were received. Approximately 200 reported that they had never seen a tumor of the lacrimal caruncle, about 100 reported cases in detail and 15 said that they had seen patients with this type of tumor but did not furnish data on individual cases. The others returned the questionnaire but failed to note whether or not they had observed any cases.

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1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2. de Schweinitz, G. E.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1924. Wood, C. A.: American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1913, vol. 2. Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936.

An analytic study of this material does not in any sense solve the problems connected with tumor of the lacrimal caruncle, but it may serve as a basis for stating them more clearly and authoritatively. The data on 200 individual cases are presented in table 1.

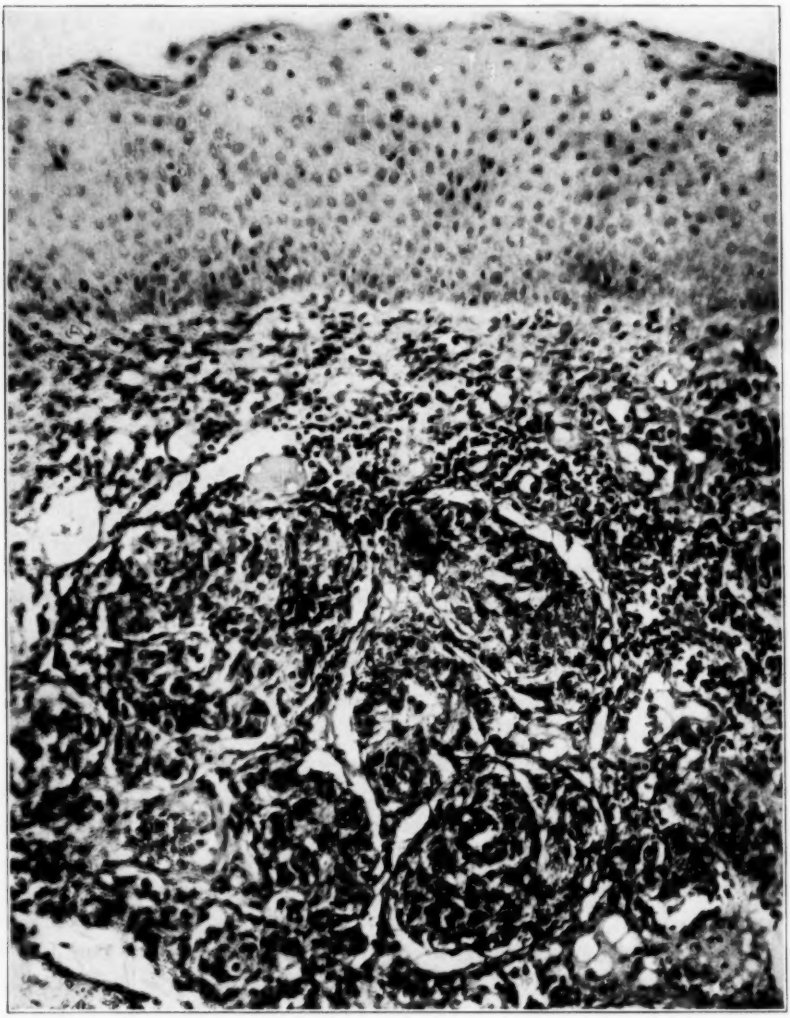

Fig. 1.—Photomicrograph of a section of melanoma of the lacrimal caruncle (author's case). Beneath the mucosal surface there is tumor tissue which in places is divided into nestlike arrangements by connective tissue septums. Throughout is a mild lymphocytic infiltration. The tumor cells are composed of various-sized nuclei, most of which contain a rather large nucleolus. The protoplasm is vacuolated, and in some there is pigment and in others a slightly eosin-staining reticulum. Mitotic figures are noted.

ANALYSIS OF MATERIAL

Classification.—The greatest difficulties were encountered in attempting to classify the data according to types of tumor. New and Erich [2] have quoted MacCallum as saying that there is no set classification of tumors and that any attempt is "only an arrangement and not a classification." If pathologists have difficulty in working out a logical classification of types of neoplasms on the basis of morphologic characteristics

Fig. 2.—Patient with melanotic tumor of the lacrimal caruncle before operation (author's case).

Fig. 3.—Patient after removal of a melanotic tumor of lacrimal caruncle (author's case).

they themselves have observed, then it may be understood that classification of material collected from such a variety of sources is practically impossible.

In arranging the cases, an attempt has been made to separate the apparently benign tumors from the malignant growths. The diagnoses

2. New, G. B., and Erich, J. B.: Benign Tumors of the Larynx: A Study of Seven Hundred and Twenty-Two Cases, Arch. Otolaryng. **28**:841-910 (Dec.) 1938.

TABLE 1.—*Data on Two Hundred Collected Cases of Tumor of the Lacrimal Caruncle*

Source	Age	Sex	Treatment	Preoperative Diagnosis	Postoperative Diagnosis	Outcome	Comment
Waite and Filmer (Massachusetts Eye and Ear Infirmary)	52	M	Sharp excision	Tumor	Angioma	Not followed	
LeWin	50	F	Excision and fulguration	.....	Hemangioma	No recurrence	
Wetzel	8	F	Excision	.....	Hemangioma	No recurrence	
Waite and Filmer	42	F	.....	Papilloma	Hemangioendothelioma	Not followed	
Downey (Army Medical Museum)	14	M	Excision	Congenital tumor	Epithelial cyst	No recurrence (2 yr.)	
Fink	42	F	Excision	Retention cyst	Retention cyst	No recurrence	
....., San Francisco	..	F	Excision	Wen	Retention cyst	No recurrence	
	..	F	Excision	Wen	Retention cyst	No recurrence	
Knapp	..	F	Excision	Sebaceous cyst	Sebaceous cyst	No recurrence	Office care
	..	F	Excision	Sebaceous cyst	Sebaceous cyst	No recurrence	Office care
McAndrews	62	M	Excision	Tumor	Sebaceous cyst	No recurrence	Present for 2 yr.; increased in size 3 mo. before operation
Friedenwald and Maumenee (Wilmer Ophthalmological Institute)	56	F	Excision	Tumor	Sebaceous glands and caruncle	No recurrence (1 yr., 3 mo.)	
Post and Saunders (Washington University)	16	F	Excision	.....	Cystic enlargement, hair follicle or sebaceous gland acinus		
Dimetry	..	..	Extirpation	.....	Cyst	No recurrence	
Behrens	52	M	None	Cyst	.....	Not followed	
Wald	20	M	Incision	Cyst, pus	.....	No recurrence	
Messinger	47	F	Desiccation	Cyst, with degeneration	.....	No recurrence	
Daily	70	F	Excision	.....	Benign, nonpigmented nevus	No recurrence	Patient died 4 yr. later from other causes
Shumway *	46	F	Excision	Nonpigmented nevus	Nonpigmented nevus	Not followed	Am. J. Ophth. **17:** 1055 (Nov.) 1934
Waite and Filmer	39	M	Removal	Papilloma	Nonpigmented nevus	Not followed	
Post and Saunders	..	F	Removal	Fibroma	Nonpigmented nevus	Not followed	
Grear (Army Medical Museum)	25	F	Excision	Melanoma	Nevus	No recurrence (18 mo.)	Present 3 yr. before operation

Reese	7	M	Excision	Nevus	Nevus	No recurrence	
	36	M	Excision	Nevus	Nevus	No recurrence	
Friedenwald (Army Medical Museum)	59	F	Excision	Tumor	Benign nevus	No recurrence	Died 4 yr. later from other causes
Hoos	23	F	Excision	Nevus	Nevus	No recurrence	
Cox	..	..	None	Nevus	.....	.....	
Lebensohn	25	F	Excision	Nevus	.. ..	No recurrence	
Jervey	8	F	Excision	Nevus	Nevus	No recurrence (5 yr.)	
Simmonds	..	..	Excision and cautery	Nevus	.....	No recurrence	
Dunnington (Reese)	19	F	Excision	.....	Pigmented nevus	No recurrence (4 yr.)	Duration, 1½ yr.
	29	F	Excision	Melanoma	Nevus	No recurrence (3 yr.)	Present for years
Waite and Filmer	43	F	Removal	?	Nevus	Not followed	
McAdams	33	F	Excision	Cystic nevus	Benign cystic nevus	Good (2 mo.)	
Perera	32	F	Excision	Nevus or fibroma	Nevus; sebaceous cyst	No recurrence (2 yr., 2 mo.)	
Flack (Reese)	..	M	Excision	Nevus	Nevus	.....	
Sallman and Knapp (Herman Knapp Memorial Eye Hospital)	55	M	Abscission	Enlarged caruncle	Nevus with inflammatory changes	.....	Present since birth; increased in size lately
	29	F	Removal	Tumor	Mole	Recurrence (15 yr.)	Large growth (3.5 by 3 cm.); cystic and translucent
	32	M	Abscission	Tumor	Nevus	.....	Present 18 yr.
Behrens	23	F	Cautery	Pigmented mole	Benign pigmented mole	No recurrence	
Hopkins	14	F	Excision	Pigmented, enlarged caruncle	Pigmented nevus	No recurrence	Pterygium also
Hosford	9	F	None	Pigmented nevus	.....	Has not changed	First observed at 6 mo.
....., Toronto	21	M	Excision	Pigmented nevus	Pigmented nevus	No recurrence	
Hosford	17	F	Excision	Melanosarcoma	Pigmented nevus	No recurrence	
Fralick (University of Michigan)	14	F	Excision	Pigmented nevus	.....	Patient died from brain tumor	First noticed at 1 yr.
Flack (Reese)	37	F	Excision	Papilloma	Pigmented nevus; hair-bearing	No recurrence (3 yr.)	Present 20 yr.; grew last 2 yr.
Friedenwald and Maumenee	26	M	Excision	Melanoma (caruncle)	Benign pigmented mole (conjunctiva)	Not followed	
Waite and Filmer	23	M	Removal	Nevus	Pigmented nevus	Not followed	
Post and Saunders	..	F	Excision	Pigmented mass	Pigmented nevus	.....	Present lifetime; increased lately
	18	F	Excision	Mass	Nevus (slightly pigmented)	.....	Duration, 1 yr.
	15	F	Excision	Tumor	Pigmented nevus	.....	Present several years
Thomas	41	M	None	Benign melanoma	.....	Little or no increase	
Meek	1	F	Excision	Pigmented nevus	Benign melanoma		
Fralick	41	F	Excision	Melanoma	Benign melanoma	No recurrence (6 mo.)	Present 3 to 5 yr.
	11	M	Excision	Pigmented nevus	Benign melanoma	Not followed	

TABLE 1.—*Data on Two Hundred Collected Cases of Tumor of the Lacrimal Caruncle—Continued*

Source	Age	Sex	Treatment	Preoperative Diagnosis	Postoperative Diagnosis	Outcome	Comment
Bruce	38	M	Excision	Melanoma	Melanoma	No recurrence (3 yr.)	Present about 20 yr.
Krimsky	24	F	Excision	Melanoma	Melanoma	No recurrence (5 mo.)	Present about 10 yr.; grew recently
Hale	About 50	M	Operation	Melanoma	.....	.....	
Hughes	About 30	M	Operation	Melanoma	Melanoma	Not followed	Clinic case
	About 30	F	Excision	Pigmented nevus	Melanoma	Not followed	
	About 30	F	Excision	Pigmented nevus	Melanoma	.....	
Moran	26	F	Excision	Melanoma	Pigmented nevus with malignant change	No recurrence (14 mo.)	Pigmented area many years; tumor occurred within 4 mo. after childbirth; pedunculated
Guy	..	F	Excision	Melanoma	.....	No recurrence	
	..	F	Excision	Melanoma	.....	No recurrence	
Ogden	3	M	Excision	Melanoma	.....	No recurrence	
	5	M	Excision	Melanoma	.....	No recurrence	
Bell	14	F	None	Melanoma	.....	Gradual decrease	
Ruedemann	About 50	F	Excision	Melanoma	Melanoma	No recurrence (3 yr.)	Present 12 to 14 yr.; grew slowly
Waite and Filmer	35	F	Removal	Melanosis oculi	Premalignant melanotic nevus	Not followed	
Dominguez (Army Medical Museum)	38	M	Excision	Tumor	Malignant melanoma, mixed type		
Evans (Army Medical Museum)	65	F	Electric cutting current	Pedunculated pigmented tumor	1. Malignant melanoma, mixed type 2. Malignant melanoma, mixed type 3. Melanotic nevus, benign ? 4. Adenocarcinoma gland of Harder 5. Embryoma, sebaceous and sweat gland elements, neuronevus, melanotic, malignant	No recurrence (2 yr.)	
Chapman *	58	M	Cold knife dissection	Melanoma	Melanocarcinoma, melanosarcoma	No recurrence locally	Death 8 yr. later; melanoma of brain (Am. J. Cancer **16**: 645, 1932)
Wetzel	23	M	Excision	.....	Melanoblastoma	No recurrence	
	28	M	Excision	.....	Melanoblastoma	No recurrence	
	36	M	Excision	.....	Melanoblastoma	No recurrence	
	76	M	Excision and exenteration	.....	Melanoblastoma, involved adjacent structures	Recurrence	Pigmentation followed burn; present 8 yr.; grew as tumor 3 yr. (Am. J. Ophth. **20**: 675, 1937)
Benedict (Mayo Clinic)	25	F	Excision	Melanoma	.....	No recurrence (2 yr., 5 mo.)	Duration, 6 mo.

Benedict (Mayo Clinic).....	53	F	None	Melanoepithelioma	.....	No increase (4 yr., 4 mo.)	Involved inner canthus, lower lid and caruncle; chronic irritation of lids; present 2 yr.
	48	F	Excision and fulguration 1,400 mg. hr. radium	Epithelioma	Melanoepithelioma, grade I	Not known	Patient died, cause unknown
	65	M	Fulguration	Melanoepithelioma	Melanoepithelioma	No recurrence (2 yr., 9 mo.)	Seen 6 wk. after operation elsewhere; growth removed from right upper lid; growth on right caruncle and conjunctiva
	45	M	Excision and cauterization; 1,400 mg. hr. radium	Carcinoma	Melanoepithelioma	Recurrence, 3 mo.; excision and cautery; 5 mo. later, exenteration and irradiation; death from visceral metastases	Two excisions for metastatic growth, right axilla
.....	43	F	Excision and cautery	Melanoma	Melanoepithelioma	No report	
Fralick.....	52	M	Excision	Melanoma	Melanoma, basal cell carcinoma	Not followed	
Johnson (Reese).....	61	F	Excision	Nevus	Melanoepithelioma	No recurrence (5 yr.)	
Ferguson.....	29	M	Excision and roentgen irradiation	Melanosarcoma	Melanosarcoma	No recurrence (6 mo.)	Small pigmented area several years before tumor grew
Dunphy.....	17	F	Excision	Melanosarcoma	Melanosarcoma	No recurrence (5 yr.)	
Smith.....	46	F	Excision	Melanotic tumor	Melanosarcoma	Several recurrences; orbit exenterated 11 mo. after excision	Growth present 29 yr.; removed elsewhere 2 yr. before; recurred and removed again 7 mo. later
Waite and Filmer.....	6	F	Dissection	Melanotic sarcoma ?	Melanotic sarcoma	Recurrence (7 yr.)	Not followed after recurrence
Moulton.....	50	F	None	Pigmented sarcoma	.....	Death	Result (?) of metastasis from sarcoma primary in abdomen
Sallman and Knapp.....	60	F	Removal	Sarcoma (upper lid)	Melanosarcoma of upper lid; origin at dark spot on caruncle	Two recurrences	
Maumenee and Friedenwald (Wilmer Institute)	5	M	Excision	Tumor	Adenoma		
	29	M	Excision	Tumor	Benign adenoma of sebaceous glands		

TABLE 1.—*Data on Two Hundred Collected Cases of Tumor of the Lacrimal Caruncle—Continued*

Source	Age	Sex	Treatment	Preoperative Diagnosis	Postoperative Diagnosis	Outcome	Comment
Veasey *	57	F	Excision	Adenoma	Cystic adenoma	.....	Minute bluish red spot (Ann. Ophth. 11 : 386, 1902)
Asbill	20	F	Excision	Skin polyp	Skin polyp	No recurrence (5 yr.)	
	13	F	Excision	Papilloma	Papilloma	Cured (5 yr.)	
Young (Army Medical Meseum)	33	M	Electrocoagulation	Verucca	Epithelial papilloma	No recurrence	
Ellett (Army Medical Museum)	7	M	Excision	Papilloma	Papilloma	No recurrence (1 yr.)	
Cox (Army Medical Museum)	22	M	Excision	Tumor	Papilloma	No recurrence (2 yr.)	Growth had been cut and cauterized 6 mo. previously; new growth, 3 weeks' duration
Waite and Filmer	53	M	Excision	Papilloma	Papilloma	Not followed	
	33	F	Excision	Papilloma	Papilloma	Not followed	
	19	F	Excision	New growth	Papilloma	No recurrence after this operation	Had recurred after previous operation
	31	M	Excision	Growth	Papilloma	Not followed	
	39	M	Excision	Growth	Papilloma	No recurrence after this operation	Had recurred after previous removal
	15	M	Excision	Growth	Papilloma	Not followed	
	30	M	Excision	Papilloma	Papilloma	Not followed	
	44	M	Removal	Papilloma	Papilloma	Not followed	
	53	F	Removal	Growth	Papilloma	Not followed	
	14	F	Removal	Malignant growth	Papilloma	Not followed	
	10	F	Removal	?	Papilloma	Not followed	
	36	M	Removal	Granuloma	Papilloma	Not followed	
Benedict	70	F	Excision and fulguration	Tumor	Papilloma	No recurrence (7 mo.)	Tumor, 2 yr. duration
Maumanee and Friedenwald	45	M	Excision and cautery	Benign papilloma	Benign papilloma	No recurrence (4 yr.)	Tumor present 1 yr.
Ball	50	M	Nitric acid cautery	Papilloma	Papilloma	One recurrence	Cured
Alvis	11	M	Excision	Papilloma	.....	Cured (12 yr.)	Present few months; 5 mm. in diameter
Pinkerton	59	M	Excision	?	Benign papilloma	No recurrence	
Brusegard	21	M	Excision	Papilloma	Papilloma	No recurrence	
Ball	45	F	Excision	Papilloma	.....	.....	Cured
Smith	24	F	Ligation	Papilloma	Papilloma	No recurrence	Pedunculated
	30	F	Ligation	Papilloma	Papilloma	No recurrence	Pedunculated
Montalvan	22	F	Excision	Papilloma	.....	No recurrence	

Simmonds	..	..	Excision and cautery	Benign papilloma	.....	No recurrence	
Guy	..	F	Excision	Papilloma	.....	No recurrence	
Metz	38	M	Excision	Papilloma	.....	Recurrence; final disappearance	Adjoining conjunctiva involved
Hosford	41	M	Excision	Papilloma	Papilloma	No recurrence	Canaliculus also involved, some lacrimation
Cullen	54	M	Cautery	Papilloma	Benign papilloma	Cure (2 yr.)	
Kennon	15	F	Excision	Papilloma	.....	No recurrence	
	..	F	Excision	Papilloma	.....	No recurrence	
	40	F	Excision	Papilloma	.....	No recurrence	
Place	39	M	Excision	Papilloma	Papilloma	Recent (2 wk.)	Growth projected between lids
Veasey *	27	M	Excision	Papilloma	Papilloma	.....	Pea-sized growth projected between lids (Ophth. Rec. **14**: 58, 1905)
	37	M	Excision	Papilloma	Papilloma	.....	Injury by piece of wood (Ann. Ophth. **20**: 85, 1911)
Perera	36	F	Excision	Papilloma	Papilloma	No recurrence (1 yr. 3 mo.)	
Kirby (Reese)	..	F	Excision	Proud flesh	Papilloma	.....	Present 1 yr.
Wheeler (Reese)	12	M	Excision	Tumor	Papilloma	Not followed	
Dunnington (Reese)	40	F	Excision	Papilloma	Papilloma	No recurrence (5 yr.)	Present more than 1 yr.
Anthony	50	F	Excision	Tumor	Nonmalignant epithelial tumor	No recurrence (6 mo.)	
Ruedemann	..	..	Excision	Epithelial overgrowth	Benign epithelial tumor		
Vail *	24	M	Excision	Tumor	Mixed tumor	No recurrence (8 yr.)	Arch. Ophth. **10**: 593 (Nov.) 1933
Waite and Filmer	18	M	Removal	Tumor		Not followed	
	28	F	Removal	Tumor	Teratoid tumor	Not followed	
					Teratoid tumor, fibrolipoma		
Ragorshek	53	F	Dissection	Cyst	Dermoid tumor	Recent (4 wk.)	
Bailey	..	F	Excision and cautery	Dermoid tumor	.....	No recurrence	
Stevenson	30	F	Dissection	Dermoid tumor	Dermoid tumor	Death 8 days after operation	Immediate orbital congestion; edema; proptosis; extension to other eye; general sepsis; destruction of both eyes; miscarriage at 5th month; death
Adelman	15	F	Excision	Dermoid tumor	Dermoid tumor, fibrolipoma	Good (6 yr.)	
Hoffman	4	F	Excision	Dermoid tumor	.....	No recurrence	
....., Toronto	48	F	Excision	Dermoid tumor	Dermoid tumor	No recurrence	
King	6	F	Excision	Dermoid tumor	Dermoid tumor of conjunctiva	No recurrence	Pathologic diagnosis by Army Medical Museum

TABLE 1.—*Data on Two Hundred Collected Cases of Tumor of the Lacrimal Caruncle—Continued*

Source	Age	Sex	Treatment	Preoperative Diagnosis	Postoperative Diagnosis	Outcome	Comment
Post and Saunders	31	M	Excision	Mass	Dermoid cyst	Recent (2 mo.)	
Smith	12	F	Dissection	Papilloma	Fibroma	No recurrence	
.....	42	M	Excision	Tumor	Fibroma	No recurrence	
Mengel	About 50	M	Excision	Fibroma	.....	No recurrence	
	About 50	M	Excision	Fibroma	.....	No recurrence	
	About 50	M	Excision	Fibroma	.....	No recurrence	
Wheeler (Reese)	41	F	Excision	Tumor	Fibromyoma	No recurrence (8 yr.)	
Wetzel	21	F	Excision	.....	Lipoma	No recurrence	
	23	F	Excision	.....	Lipoma	No recurrence	
Montalvan	28	F	Excision	Dermolipoma	.....	No recurrence	
Jones	About 70	M	Excision	Fatty polypoid	.....	No recurrence	
Reed	About 30	M	Excision	Lymphoma	.....	Unknown	
Thorne	22	F	Incision and blunt dissection	.....	Adventitious lymph node	.....	Pathologic diagnosis by Verhoeff
Good	46	F	Coagulation	.....	Granuloma	No recurrence	
Waite and Filmer	16	M	Removal	Granuloma	Granuloma, lymphoid	Not followed	
Maumenee and Friedenwald	23	F	Excision	Tumor	Granuloma	No recurrence (3 yr.)	
Fralick	9	M	Excision	Pigmented nevus	Cellular nevus neurofibroma, locally infiltrating	Growth (2½ yr.) involves medial half upper and lower lids and globe	Present since birth; exenteration advised, but parents refused
....., New York	56	M	Excision and roentgen irradiation	Carcinoma	Carcinoma	No recurrence (1½ yr.)	

Asbill	60	F	Roentgent irradiation	Carcinoma (?)	.....	Not followed	Unpigmented mole present many years, grew suddenly; hard, lobulated, with broad attachment
Zubak	56	M	Roentgen and radium irradiation	Carcinoma	.....	Vision still good; patient refuses exenteration	Clinic case
Holland	72	M	Excision and cautery	Carcinoma	Carcinoma, low grade	No recurrence (4 yr.)	Injury to eye by piece of wire
Capps	59	F	Excision and irradiation	Carcinoma	.....	Recurrence treated with roentgen rays	Operated on elsewhere; treated for recurrence
Cullen	59	M	None	Carcinoma	.....	Unknown	Seen 4 yr. after operation elsewhere, with recurrence; refused more treatment
Bailey	..	M	Excision and cautery	Epithelioma	.....	Not followed	
Wheeler	72	F	Diathermy	Epithelioma	Epithelioma	No recurrence (6 yr.)	
Larsen	About 60	M	Excision	Epithelioma	.....	No recurrence (5 yr.)	
Weeks	70	M	Thermoradiotherapy	Epithelioma	.....	No recurrence (3 yr.)	Involved corneal conjunctiva and caruncle; caruncle probably secondary
Kiehle	56	M	None	Epithelioma	.....	.....	Refused treatment
Bouvy	..	F	Excision and radium	Tumor	Epithelioma	Recurrence	
Dimetry	..	..	Extirpation	.....	Epithelioma	No recurrence	
	..	..	Extirpation	.....	Epithelioma, malignant	No recurrence	
Waite and Filmer	74	M	Wide excision	Papillary carcinoma	Epithelioma	Not followed	
Foucar (Army Medical Museum)	68	M	Enucleation exenteration; radium	Epidermoid carcinoma	Epidermoid carcinoma	Death 2 days after operation	
Messinger	63	M	Excision and roentgen irradiation	Carcinoma	Epidermoid carcinoma	No recurrence	
Davis	77	M	Biopsy	Squamous carcinoma	1. Epidermoid carcinoma 2. Basal cell carcinoma 3. Squamous carcinoma (conjunctiva)	Not known	Present 1 mo.

TABLE 1.—*Data on Two Hundred Collected Cases of Tumor of the Lacrimal Caruncle—Continued*

Source	Age	Sex	Treatment	Preoperative Diagnosis	Postoperative Diagnosis	Outcome	Comment
Good	70	F	Operation	.....	Broad cell carcinoma	Recurrence treated with radium	
Savage	..	..	Excision	.....	Sarcoma	Recurrence (16 yr.)	Patient lost eye
....., San Francisco	..	F	Excision	.....	Sarcoma, nonpigmented	No recurrence (6 yr.)	
Veasey *	26	M	Excision	.....	Sarcoma	No recurrence (1 yr.)	Grew in 7 wk. from size of pinhead to that of small pea (Arch. Ophth. **26**: 204, 1897)
Sallman and Knapp	35	M	Excision	Polypoid, pedunculated mucous growth	Adenosarcoma	.....	Present 6 mo.; another tumor removed 36 yr. later; no details available
Paton	..	..	Excision	.....	Diffuse cellular tumor, either low grade round cell sarcoma or tumor of nevus cells		
Maumenee and Friedenwald	29	M	Excision	Papilloma	Peculiar tumor, probably benign; large round cells	No recurrence (2 yr.)	
Sallman and Knapp	50	M	Excision	Tumor	Dense round cell infiltration of submucosa	.....	Onset of swelling sudden 4 wk. before operation
Hughes	10	F	Excision	Tumor	Collection of fibrous tissue	No recurrence	
Zubak	..	F	Electrocoagulation	Hypertrophy	.....	No recurrence	
	..	F	Electrocoagulation	Hypertrophy	.....	No recurrence	
	..	F	Electrocoagulation	Hypertrophy	.....	No recurrence	
Rosenbaum	14	F	None	Enlargement, 4 to 5 times	.....	No change in size (8 yr.)	
Waldstein	..	..	Excision	Benign tumor	.....	No recurrence	
	..	..	Excision	Benign tumor	.....	No recurrence	
Ravdin	42	F	Excision and cautery	Benign tumor	.....	No recurrence	
Buchanan	28	M	None	Benign tumor, congenital	.....	Remained stationary	Refused treatment
....., Springfield, Mass.	50	F	Excision	Benign tumor	.....	No recurrence	

* Case previously published. Reference furnished under "Comment."

Note: Some contributors failed to sign their names and hence are not listed in this table. Their contributions are listed as ....., with the place name, derived from the postmark.

furnished have been used in all instances, and the grouping of cases in table 2 is in accordance with suggestions made by Dr. A. B. Reese.

Incidence.—From the material collected, it is impossible to make any definite statement as to the incidence of tumors of the lacrimal caruncle in ophthalmic practice. Some physicians furnished information as to the approximate number of patients they had seen, while others told only the number of years they had been in practice. Although it would appear that these tumors are considerably less rare than the reports in the literature would indicate, they are by no means of frequent occurrence.

TABLE 2.—*Grouping of Tumors of the Lacrimal Caruncle*

Group	Diagnoses	No. of Cases
I	Angioma	1
	Hemangioma	2
	Hemangioendothelioma	1
II	Cyst	4
	Epithelial cyst	1
	Retention cyst	3
	Sebaceous cyst	5
III	Nevus	15
	Nonpigmented nevus	4
	Pigmented nevus	13
	Cystic nevus	3
	Benign melanoma	4
	Malignant melanoma	4
	Melanoma	12
	Melanoblastoma	6
	Melanoepithelioma	7
	Melanosarcoma	6
IV	Adenoma	3
V	Skin polyp	1
	Papilloma	40
	Benign epithelioma	2
VI	Mixed tumor	1
	Teratoid	2
VII	Dermoid	8
VIII	Fibroma	5
IX	Fibromyoma	1
X	Lipoma	2
	Dermolipoma	1
XI	Lymphoma	1
	Adventitious lymph node	1
XII	Granuloma	3
XIII	Pigmented neurofibroma	1
XIV	Carcinoma	6
	Epidermoid carcinoma	3
	Broad cell carcinoma	1
	Epithelioma	9
XV	Sarcoma	3
	Adenosarcoma	1
Miscellaneous	Benign round cell tumor	3
	Fatty polypoid	1
	Fibrous tissue	1
	Hypertrophy	4
	Benign tumor	5

The series of approximately 200 cases collected here has been culled from an aggregate experience which must encompass several million patients. Many oculists of wide experience and reputation report that they have never seen a case of tumor of the caruncle. A number of prominent pathology laboratories have no record of such a tumor. The largest series reported in some detail by a physician in private practice was 8, although one or two men, who furnished no data on individual cases, said that they had seen 15 or 20. The greatest number of cases reported by an institution was from the Massachusetts Eye and Ear Infirmary, with details concerning 23. Twelve additional cases of tumor of the lacrimal caruncle had been observed in private services. Only 8 of the cases collected in this study had been reported previously in the medical literature.

Age.—Table 3 shows the age incidence in this series of cases. The patients are fairly evenly distributed through the first six decades of life, with the greatest numbers in the third, fifth and sixth decades.

Sex.—The distribution between the sexes is fairly even, with 83 males and 104 females in the cases in which the sex was designated.

Etiologic Factors.—Although injury and irritation have been mentioned in a good many reported cases of tumor of the lacrimal caruncle, this factor was mentioned specifically by those answering the questionnaire in only 3 instances. In 1 case in which the pathologic diagnosis was low grade carcinoma, the patient gave a history of having injured his eye with a piece of wire several years earlier. In the case reported by Wetzel [3] the patient had burned his eye with hot grease, and this injury was followed by pigmentation which, after a period of years, developed into a tumor which was diagnosed as melanoblastoma. In a

TABLE 3.—*Age Incidence*

Age	No. of Cases
1 to 10	13
10 to 20	25
20 to 30	32
30 to 40	28
40 to 50	21
50 to 60	30
60 to 70	9
More than 70	10

case of papilloma, reported by Veasey,[4] the eye had been injured by a piece of wood before development of the tumor.

The only answer which indicated that climate might have an influence on the growth of these tumors was that of Gill, of San Antonio. He said: "Simple swelling or tumefaction of the caruncle from irritation, sunlight, alkali dust, heat, etc., is very frequently encountered here." He also noted that there is a rather high incidence of malignant degeneration of pterygia at their apex and that pterygia are frequent in the climate of San Antonio.

With reference to 16 cases in this series, special comment was made that a small pigmented area had been noted on the caruncle which remained stationary for several years and in some instances for many years before rapid tumor growth occurred.

In 2 instances the growth of the tumor coincided with pregnancy, and in 1 of these cases removal of the tumor resulted fatally.

3. Wetzel, J. O.: Melanoblastoma of the Lacrimal Caruncle: Report of a Case and Review of the Literature, Am. J. Ophth. **20**:675-689 (July) 1937.

4. Veasey, C. A.: Some Unusual Ophthalmic Cases, Ann. Ophth. **20**:80-85 (Jan.) 1911.

Treatment.—The treatment of tumor of the caruncle presents no special problem, because the growth can be excised surgically or by means of the electric cautery. In most of the cases in this series the tumor was removed by surgical dissection. In some cases cautery was applied after removal of the growth, and roentgen or radium irradiation was used, sometimes as a precautionary measure, and at other times to treat recurrences or extensions of the process. In 5 cases in which pathologic examination showed a high degree of malignancy or in which there was invasion of the globe, exenteration was done.

Prognosis.—The preponderant number of tumors of the lacrimal caruncle apparently are benign, and even those which are diagnosed as malignant do not show a great tendency to recurrence or metastasis. Recurrence locally was reported in 12 instances in this series. In most of these the tumor recurred several years after its first removal; in 1 case it recurred sixteen years after and in another thirty-six years. Fralick, of the University of Michigan, reported extension and invasion of other orbital tissues in a young boy, but the parents refused to allow removal of the eye. In 1 case, previously reported by Chapman,[5] the subsequent history shows that the patient lived eight years after removal of the primary melanoma of the caruncle but died from metastatic involvement of the brain by a melanotic growth. Benedict reported 1 case in which there was local recurrence and distant metastases. Metastatic lesions in the axilla necessitated two excisions, and the patient died eventually of visceral metastases.

There were only 2 postoperative deaths in this series. One followed the removal of a dermoid tumor from a young woman who was pregnant, and the other occurred in a man, aged 68, after the removal of an epidermoid carcinoma.

REVIEW OF THE LITERATURE

In this study no attempt will be made to review completely the literature on tumors of the lacrimal caruncle. In 1928 Serra[6] collected 136 cases from the literature, including cases of epithelioma, sarcoma, melanoma, fibroma, polyp, angioma, papilloma, adenoma, dermoid tumor, dermoid cyst, mixed tumor, simple hypertrophy, lymphoma, granuloma and simple cyst. Since his review, Vail,[7] Wetzel,[3] Chapman[5] and

5. Chapman, V. A.: Melanoma of the Caruncle, Am. J. Cancer **16**:645-649 (May) 1932.

6. Serra, G. M.: Tumori della caruncola lacrimale: Studio clinico ed anatamo-patologico-casistica, Boll. d'ocul. **7**:783-864, 1928.

7. Vail, D. T., Jr.: Mixed (Teratoid) Tumors of the Lacrimal Caruncle, Tr. Sect. Ophth., A. M. A., 1933, pp. 175-185; Arch. Ophth. **10**:593-601 (Nov.) 1933.

Shumway [8] have reported cases in American periodicals, and in Europe, especially in Italy, a number of contributions on tumor of the caruncle have been published. Most of these are based on individual case reports, with a review of some of the literature (Aliquo Mazzei,[9] Sgrosso,[10] Wendlberger,[11] Casanovas,[12] Tirelli,[13] Pergola,[14] Busacca,[15] Agnello,[16] Lumbroso,[17] Motolese,[18] Alexiadès [19] and Terrien and Veil [20]). The cases of Vail, Wetzel, Chapman and Shumway are included in the series collected for this study. Vail reviewed the literature on mixed tumors of the lacrimal caruncle, and Wetzel analyzed previously reported cases of melanotic tumor.

COMMENT

According to Wolff,[21] the caruncle is developed by the cutting off of a portion of the lower lid by the growth of the lower canaliculus. It is a small, fleshy-looking, ovoid body some 5 mm. in height and 3 mm. broad, situated in the lacus lacrimalis to the inner side of the plica semilunaris. It is attached to the plica, and fibers of the internal rectus sheath enter its deep surface.

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8. Shumway, E. A.: Nonpigmented Nevus of the Lacrimal Caruncle, Am. J. Ophth. **17**:1055-1057 (Nov.) 1934.

9. Aliquo Mazzei, A.: Contributo istologico alla conoscenza dei tumori della caruncola lacrimale, Atti d. r. Accad. d. fisiocrit. di Siena **4**:520-534 (Dec. 30) 1929.

10. Sgrosso, S.: Sull'amartoma della caruncola lagrimale, Arch. di ottal. **41**:90-104 (Jan.-Feb.) 1934.

11. Wendlberger, J.: Gutartige und bösartige Tumoren nebst Nevi, Dermat. Ztschr. **78**:95-111 (July) 1938.

12. Casanovas, J.: Melanoma de la caruncola, Arch. de oftal. hispano-am. **35**: 71-74 (Feb.) 1935.

13. Tirelli, G.: Melanoma della caruncola lacrimale, Rassegna ital. d'ottal. **1**: 948-959 (Nov.-Dec.) 1932.

14. Pergola, A.: Contributo clinico ed istopatologico allo studio dei polipi angiomatosi della caruncola lacrimale, Rassegna ital. d'ottal. **4**:782-792 (Nov.-Dec.) 1935.

15. Busacca, A.: Sui tumori pigmentati della caruncola lacrimale (Studio clinico ed histologico), Rassegna ital. d'ottal. **4**:502-520 (July-Aug.) 1935.

16. Agnello, F.: Sul papilloma della caruncola, Rassegna ital. d'ottal. **7**: 553-559 (July-Aug.) 1938.

17. Lumbroso, U.: Fibro-emangioma della caruncola (Contributo clinico ed istologico), Rassegna ital. d'ottal. **2**:198-210 (March-April) 1933.

18. Motolese, F.: Sarcoma primitivo della caruncola lacrimale, Boll. d'ocul. **13**:1433-1442 (Nov.) 1934.

19. Alexiadès: Un cas de sarcome primitif de la caroncule lacrymale et du pli sémi-lunaire, Arch. d'opht. **48**:341-347 (May) 1931.

20. Terrien, F., and Veil, P.: Etude anatomo-clinique d'un cas de naevo-cancer de la caroncule, Bull. et mém. Soc. franç. d'opht. **49**:106-113, 1936; Arch. d'opht. **53**:721-728 (Oct.) 1936.

21. Wolff, E.: The Anatomy of the Eye and Orbit, Philadelphia, P. Blakiston's Son & Co., 1936.

The caruncle is really a piece of modified skin, so is covered by modified stratified epithelium and is supplied with hairs and sebaceous and sweat glands. It develops from the skin, containing glands like those of Krause. The epithelium resembles that of the margin of the lids. At its junction with the conjunctiva, however, goblet cells are found. The sebaceous glands resemble those of Zeis and Meibomius. They produce the characteristic white secretion frequently found at the inner canthus. The modified lacrimal glands are often conspicuous structures. They do not represent the gland of Harder, which is absent in the human being. The hairs, about fifteen in number, are fine and colorless and directed toward the nose. The blood supply is from branches from the central palpebral artery. These vessels pass (like those of the scalp) through dense connective tissue which prevents them from contracting when cut; they gape, and free hemorrhage results. The lymphatics pass to the submaxillary glands. The nerve supply is from the infratrochlear nerve.

Because it is composed of modified skin, the caruncle contains a variety of cells of both ectodermal and mesodermal origin. It follows, at least theoretically, that any of these elements, alone or in combination, can proliferate to form a neoplasm. Hence it is not at all surprising that so many types of tumors of the lacrimal caruncle have been described.

The statement of Wolff,[22] Parsons [23] and Atkinson [24] that papilloma is the most common tumor of the caruncle is in a measure confirmed in the series of cases collected for this study, when a single diagnosis is taken into account, for the diagnosis in 42 cases was papilloma or benign epithelial tumor. The pigmented tumors, however, including those diagnosed as nevus, pigmented nevus, benign melanoma, melanoma, melanoblastoma, melanocarcinoma and melanosarcoma, number 73 and hence represent a much larger group than the papillomas. There is also the probability that some of the tumors listed as papilloma, carcinoma, epithelioma or sarcoma were pigmented, although this was not indicated in the reports. The preponderance of pigmented tumors in this series is interesting in view of Martin's [25] statement that the incidence of melanoma among cases of cancer of the eyelids is so small as to have no influence on the statistics.

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22. Wolff, E.: A Pathology of the Eye, Philadelphia, P. Blakiston's Son & Co., 1935.

23. Parsons, J. H.: The Pathology of the Eye, New York, G. P. Putnam's Sons, 1904, vol. 1.

24. Atkinson, D. T.: External Diseases of the Eye, Philadelphia, Lea & Febiger, 1934.

25. Martin, H. E.: Cancer of the Eyelids, Arch. Ophth. **22**:1-20 (July) 1939.

From the series of cases reported here, it would appear that melanotic tumors of the caruncle are more benign than melanoma generally, which is regarded by many authorities as one of the most malignant of neoplasms (Adair;[26] Nathanson and Welch[27]). In only 2 instances was metastasis reported, and in 1 this did not occur until eight years after the primary growth had been removed. Several authors (Adair;[26] Broders and McCarthy[28]) have commented that melanoma of the skin is more malignant than that of the eye. Since the caruncle is composed of modified skin, it might be expected that a high degree of malignancy would be shown by melanoma in this region, but this is not confirmed by the facts elicited in this study.

What is the explanation for the apparently benign nature of pigmented tumors of the caruncle? Is this due to their anatomic situation, or is the answer to be found in the histologic structure of the growths? Is the deposit of melanin in these tumors merely coincidental, because the skin and the eyes are the most highly pigmented structures of the body, or does it represent an actual proliferation of melanin-producing cells? What are the histologic criteria for predicting the benign or malignant nature of a pigmented growth?

The answers to these and many other questions regarding melanotic tumors are still obscure. From the pathologic standpoint, the pigmented tumors furnish a most interesting field for study and speculation. Ewing (Becker[29]) has said: "The peculiar and obscure conditions of the origin of melanoma, the remarkable physiologic properties of the chromatophores in the animal kingdom and the eccentricities of its clinical course, and its interesting history as a field of debate render this tumor one of the most notable topics in oncology."

Much of the confusion regarding pigmented tumors arises from the fact that there is no agreement among histologists as to the type of cell which produces or contains melanin. There are those who claim that a distinction must be made between the cells that produce melanin and those which simply absorb or carry this pigment. Others insist that all cells that contain melanin are of a single type, but they are not in agreement as to what this single type of cell is. More conservative pathologists are inclined to the view that both ectodermal and mesodermal

26. Adair, F. E.: Treatment of Melanoma: Report of Four Hundred Cases, Surg., Gynec. & Obst. **62**:406-409 (Feb., no. 2A) 1936.

27. Nathanson, I. T., and Welch, C. E.: Life Expectancy and Incidence of Malignant Disease, Am. J. Cancer **31**:598-608 (Dec.) 1937.

28. Broders, A. C., and McCarthy, W. C.: Melano-Epithelioma: Report of Seventy Cases, Surg., Gynec. & Obst. **23**:28-32 (July) 1916.

29. Becker, S. M.: Cutaneous Melanoma: A Histologic Study Especially Directed Toward the Study of Melanoblasts, Arch. Dermat. & Syph. **21**:818-835 (May) 1930.

elements, which may be extremely difficult to differentiate, are involved in melanotic neoplasms and hence believe that they should be called melanomas or melanoblastomas (Becker,[29] Coley and Hoguet,[30] Wetzel [3] and Reese [31]). Goldstein and Wexler [32] have stated: "The relation of the chromatophores to nevomelanoma is not clear; yet theoretical considerations favor the origin of all melanomas from mesoblastic chromatophores, while the histology of tumors favors their origin from epithelial cells which have taken on pigmentary functions." Until recently, apparently most pathologists regarded melanotic tumors and nevi as of mesodermal origin (Stoewer,[33] Handley,[34] Ribbert,[34] Fuchs,[35] Wintersteiner,[35] Foster,[35] Graeff [35] and Axenfeld [35]).

A newer conception, and one which many pathologists are inclined to accept, is that they are of ectodermal origin (Unna,[35] Knight,[36] Broders and McCarthy [28] and Wagener and Wellbrock [37]). Masson [38] has gone further and stated definitely that pigment-producing tumors and nevi arise from the Schwann cells of the neural sheath. Foot [39] and Dvorak-Theobald [40] have confirmed this opinion, and Jacobsen and Klinck [41] have gone so far as to state: "Whenever a pigment can reasonably be assumed to be melanin, its origin from cells of the neuro-ectodermal origin is quite definitely indicated. Hence we feel . . . . the time has come to state unequivocally that melanin itself, no matter where it is found, is always of neurogenic origin." On the other hand,

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30. Coley, W. B., and Hoguet, J. P.: Melanotic Cancer, with Report of Ninety Cases, Tr. Am. S. A. **34**:319-383, 1916.

31. Reese, A. B.: (*a*) Precancerous Melanosis and Diffuse Malignant Melanoma of the Conjunctiva, Arch. Ophth. **19**:354-365 (March) 1938; (*b*) Intra-Ocular Tumors, South. Surgeon **7**:194-203 (June) 1938.

32. Goldstein, I., and Wexler, D.: Melanosis Uveae and Melanoma of the Iris in Neurofibromatosis (Recklinghausen), Arch. Ophth. **3**:288-296 (March) 1930.

33. Cited by Wetzel.[3]

34. Cited by Coley and Hoguet.[30]

35. Cited by Shumway.[8]

36. Knight, M. S.: Melanotic Neoplasms of the Eye, J. A. M. A. **83**:1062-1068 (Oct. 4) 1924.

37. Wagener, H. P., and Wellbrock, W. L. A.: Benign Melanoma and Melano-Epithelioma of the Choroid, Arch. Ophth. **4**:509-515 (Oct.) 1930.

38. Masson, P.: Giant Neuro-Naevus of the Hairy Scalp, Ann. Surg. **93**:218-222 (Jan.) 1931.

39. Foot, N. C.: Concerning the Histology of Melanoma, with Special Consideration to the Nervous Elements of the Tumor, Am. J. Path. **8**:321-328 (May) 1932.

40. Dvorak-Theobald, G.: Neurogenic Origin of Choroidal Sarcoma, Arch. Ophth. **18**:971-997 (Dec.) 1937.

41. Jacobsen, V. C., and Klinck, G. H., Jr.: The Mobilization and Excretion of Melanin in Normal and Pathological Conditions, Am. J. Path. **9**:948-949 (Nov.) 1933.

Ebert,[42] who made a careful histologic study in a case of multiple melanotic nevi, while inclined toward Masson's view of the schwannian origin of nevus cells, is not entirely convinced that this theory is correct and has stated that the subject needs more investigation.

Recently, Robertson [43] has made an interesting suggestion that the melanomas may arise from the hair follicular layer of the epidermis, perhaps from the matrix cells of the medulla, and that the term trichinoma might well be added to the nomenclature of tumors. He also stated that most so-called basal cell tumors are derived from this layer of the epithelium.

It is not within the scope of this paper to discuss in detail these various theories of the origin of melanotic tumor, nor am I capable of an authoritative opinion concerning them. Until such time as there can be some general agreement among pathologists as to the derivation of these neoplasms, it would seem that they should be designated simply as melanomas, or melanoblastomas, and that pathologists and ophthalmologists should collaborate to develop criteria for distinguishing, so far as possible, the benign from the malignant growths. For this is the problem which is of clinical importance in the management of the individual case.

Although, so far as is known, the method has not been applied to the study of tumors of the caruncle, the investigations of Callender and Wilder [44] may prove valuable in this connection. They have worked out a classification of malignant melanomas of the choroid and ciliary body on the basis of cell type and the degree of silver staining of reticulum fibers and have correlated this with the results in 253 cases five years after enucleation, in order to evaluate their technic as a basis for prognosis. They recognize four cell types: (1) spindle cell, with subgroups A and B; (2) epidermoid, (3) vascular, and (4) mixed cell. They found that the epidermoid cell type appears to be the most malignant and the spindle cell type A relatively benign. The mixed group, which in almost all cases contained epithelioid cells, is second in malignancy to the purely epithelioid tumor. In the classification of fiber

42. Ebert, M. H.: Multiple Pigmented Nevi: Study of Origin of Nevus Cell, Arch. Dermat. & Syph. **37**:1-21 (Jan.) 1938.

43. Robertson, H. E.: Tumor Nomenclature: Suggestions for Its Revision, Am. J. Clin. Path. **9**:24-35 (Jan.) 1939.

44. Callender, G. R.: Malignant Melanotic Tumors of the Eye: Study of Histologic Types in One Hundred and Eleven Cases, Tr. Am. Acad. Ophth. **36**: 131-142, 1931. Wilder, H. C.: An Improved Technique for Silver Impregnation of Reticulum Fibers, Am. J. Path. **11**:817-819 (Sept.) 1935. Callender, G. R., and Wilder, H. C.: Melanoma of the Choroid: The Prognostic Significance of Argyrophil Fibers, Am. J. Cancer **25**:251-258 (Oct.) 1935. Wilder, H. C., and Callender, G. R.: Malignant Melanoma of the Choroid, Am. J. Ophth. **22**:851-855 (Aug.) 1939.

content, malignancy of the tumor appears to be inversely proportional to the degree of intracellular invasion by argyrophil fibers. These authors have concluded that the two classifications used in conjunction definitely narrow the field of error in the prognosis of uveal melanoma.

Another investigation which may shed some light on the malignancy of nevi and melanotic tumors is that of Greenblatt, Pund and Bernard,[45] who studied a series of 250 nevi to determine the histologic picture in the development from benign to malignant types. They apologized for the use of the term borderline but admitted that in some instances it could not be avoided. These authors recognized the following types of nevi: quiescent nevus, the aggressive nevus, borderline melanoma, low grade malignancy and advanced malignancy. These types show progressively a histologic picture of quiescence, cellularity, cellular cohesion, extension, abnormal cellular activity, stroma reaction, invasion, mitosis and metastasis.

Since the development of malignant melanoma from preexisting pigmented nevi or melanotic areas has been stressed by numerous authors, and since occurrences of this type were reported in a significant proportion of the cases collected in this series, it would appear that a careful investigation, both clinical and histologic, of all nevi of the caruncle, might be fruitful in contributing to the knowledge of this type of tumor. Affleck,[46] in a study of 317 cases of malignant melanoma from all parts of the body, discovered that 266 developed from previously existing quiescent nevi but noted that in the same series there was no instance of melanoma developing from a hairy mole. Wagener and Wellbrock [37] reported a case of melanoma of the choroid in which histologic examination revealed a definite preexisting benign melanoma within which the malignant growth began. Miescher [47] reported that of 35 malignant melanomas of the skin, 15 arose from a nevus, 10 from normal skin and 10 from precancerous melanosis.

Reese [31a] has contributed an excellent study on malignant melanomas arising from premalignant melanosis of the conjunctiva, which he described as a rather diffuse nonelevated pigmentation in otherwise normal-appearing tissue, of granular appearance, with confluence of the granules to form more or less dense sites of pigmentation. He stated that a nevus of the conjunctiva is not an obligatory precancerous lesion, whereas acquired melanosis ultimately becomes malignant. In contrast to the diffuse flat character of the melanotic lesion which develops from

45. Greenblatt, R. B.; Pund, E. R., and Bernard, G. T.: Benign Nevus; Malignant Melanoma; Problem of Borderline Case, South. M. J. **29**:122-129 (Feb.) 1936.

46. Affleck, D. H.: Melanomas, Am. J. Cancer **27**:120-138 (May) 1936.

47. Miescher, cited by Reese.[31a]

precancerous melanosis, the malignant melanoma arising from a nevus grows more as a localized tumor mass. Reese noted also that besides an increase in size and pigment content the onset of malignant growth in an area of melanosis is frequently accompanied by signs and symptoms of inflammation. He has commented that, judging by the microscopic appearance, processes of procession and regression sometimes go hand in hand, so that clinically a changing picture, as regards pigmentation, might be produced, and hence that the degree of pigmentation would not necessarily be an accurate criterion of the activity of the process.

In regard to this last point, Benedict [48] stated:

> The depth of pigmentation is sometimes taken as an indication of the rate of growth of a tumor or as a measure of its degeneration, but many fallacies appear in such consideration. Pigmentation may be attributable to melanin in or between chromatophores or to melanin mixed with blood pigment from hemorrhages or from spaces containing stagnant blood. . . . A primary tumor may be heavily pigmented, a recurrent tumor only lightly so, and the metastatic growths may contain little or no pigment. As the pigment is not an integral part of the tumor, but only a secondary invader, the depth of pigmentation may indicate the age or relative rate of growth. . . . In general, it was observed that tumors that contained the greatest amount of pigment were the least malignant from the standpoint of the presence of mitotic figures and of metastasis, while the most extensive metastatic tumors contained little or no pigment.

This raises the question as to the determination of melanotic lesions that do not exhibit gross pigmentation. Adair [26] has commented that the nonpigmented melanotic tumors are usually not recognized before operation and consequently are badly handled. The so-called dopa reaction, devised by Bloch,[49] has been utilized by many investigators to detect the presence of melanin-producing cells, and no doubt the employment of this technic in the study of nonpigmented neoplasms of the caruncle and other ocular tissues would contribute information of value. Ebert [42] has asserted that all nevus cells give a positive dopa reaction in the earliest stages. According to Miescher,[49] the oxidative ferment, which converts dopa to melanin, is present only in embryonic cells, and normal pigmented cells are mere carriers of pigment during ordinary adult life. If there is any process of malignant degeneration, the cells return to their original character, and the dopa reaction again becomes positive. Hence he regards a dopa-positive reaction as unmistakable proof of the presence, not of pigment, but of the process of pigment formation, and hence of abnormal cellular activity.

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48. Benedict, W. L.: Clinical Considerations of Melanotic Neoplasms of the Eye and Orbit, Surg., Gynec. & Obst. **64**:513-516 (Feb., no. 2 A) 1937.

49. Cited by Dvorak-Theobald.[40]

SUMMARY AND CONCLUSIONS

Analysis of a series of 200 cases of tumor of the lacrimal caruncle collected from the files of ophthalmologists throughout the country shows: 1. While these lesions are of rare occurrence they are more frequent than previous reports would indicate. 2. Although papilloma is the commonest single diagnosis, the pigmented tumors comprise the largest group of tumors in this series (approximately 35 per cent). 3. The nomenclature of tumors in this area is hopelessly confused. 4. The preponderance of tumors of the lacrimal caruncle are benign, but a small proportion are malignant and display a tendency to recurrence and metastasis, and any pigmented tumor must be regarded as at least potentially malignant. 5. There are no reliable criteria for accurate classification of benign and maligant tumors, especially those that are pigmented. 6. For these reasons, the prognosis in individual cases cannot be made with any degree of precision.

Since the experience of the individual ophthalmologist with tumors of the caruncle is usually limited to 1 or 2 cases in a lifetime of practice, it would appear that the only way that information of value concerning this condition is to be acquired is by collective, collaborative effort. If the persons who encounter cases of tumor of the lacrimal caruncle would take advantage of the facilities of the American Institute of Pathology, which is operated under the auspices of the National Research Council in connection with the Army Medical Museum, a significant mass of material might be accumulated. In this way, careful clinical records and observations, including follow-up of cases, might be correlated with detailed and consistent histologic study, in order that information of practical value to the ophthalmologist might be acquired.

The clinical information should include a careful history, with special reference to the presence of trauma or irritation, and a preexisting nevus or pigmented area as well as the duration of the growth. The appearance of the lesion should be recorded accurately, including its size, whether or not it is flat or elevated, the degree and character of pigmentation, the presence or absence of inflammation or granulation and the type of attachment at the base. At regular follow-up examinations, which should continue for a period of years, the appearance of the area should be noted and evidence of recurrence or metastases recorded in detail. One point which such study might elucidate is the effectiveness of irradiation in cases of malignant growths, about which there is considerable doubt at present. Some authors claim that melanotic tumors are radioresistant, while others have reported favorable results in cases of precancerous and malignant melanoma. The statement has also been made that radiosensitivity is inversely proportional to the degree of pigmentation.

Pathologic examination, in addition to routine microscopic examination of cellular structure by a pathologist familiar with the anatomy of the eye, might include in selected cases the employment of certain special technics, such as that described by Callender and Wilder and the dopa reaction.

In the pathologic arrangement and classification of tumors of the caruncle, an effort should be made, first of all, to determine whether the growth is a true neoplasm or of inflammatory origin. As New and Erich [2] have pointed out, in discussing tumors of the larynx, this is by no means a simple matter in all cases. If the growth is a true neoplasm, an effort should be made to determine whether it is malignant, whether or not it contains melanin and, finally, the type or types of cells of which it is composed.

If all these data had been available on the group of cases represented in this collected series, it might have been possible to draw more definite conclusions regarding the clinical classification of caruncular tumors. Hence an appeal is made to all ophthalmologists to study carefully and to record in detail the observations on the few cases of this and other rare conditions, in order that by collaboration the resulting aggregate experience may teach the entire profession something of value.

The names of contributors and correspondents who supplied data on which this paper is based will appear in the reprints.

PERSPECTIVES IN GLAUCOMA RESEARCH

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The turn of the century which marked the beginning of Dr. Verhoeff's career as an ophthalmologist was notable also for the publication of Leber's [1] great monograph on the nutrition of the eye. This book was the climax of Leber's contributions to the understanding of the intraocular fluid exchange and, in a sense, marked the end of the classic period of research on glaucoma. It is refreshing even now to reread this lucid and far seeing exposition and to recapture something of the excitement which these studies must have had for the young student of those days. The culmination of Leber's work marked the completion of a cycle of anatomic and physiologic studies begun a generation earlier, but it was also the beginning of a new period in which biochemical methods and arguments were to struggle slowly to the fore.

PHYSICOCHEMICAL FACTORS IN THE FORMATION OF THE AQUEOUS

It is difficult to set a date of beginning for these chemical studies, but one of the first triumphs in this field was that of Wessely [2] concerning the distribution of fluorescein between blood and aqueous. He was able to show that the concentration of the dye in the aqueous becomes equal to that of the free, i. e., diffusible, fraction in the blood, as determined by ultrafiltering blood through semipermeable membranes. Hence it was concluded that the thermodynamic forces concerned in the equilibrium of crystalloids and colloids across semipermeable membranes were likewise concerned in the formation of the intraocular fluid. Further studies by a great many different workers eventually showed that the composition of the aqueous fluid resembled that of the nonprotein fraction of the blood plasma. These findings raised the question: How far can the composition of the intraocular fluid be accounted for solely by these thermodynamic forces?

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1. Leber, T.: Die Cirkulations-und Ernährungsverhältnisse des Auges, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1903, vol. 2, pt. 2.

2. Wessely, K.: Der Flüssigkeits-und Stoffwechsel des Auges mit besonderer Berücksichtigung seiner Beziehungen zu allgemeinphysiologischen und biologischen Fragen, Ergebn. d. Physiol. **4**:565, 1905.

This question at issue merits, perhaps, more explicit statement. Thermodynamic forces, i. e., forces of diffusion and osmosis arising from the activities of solutes in solution, are universal. Two bodies of fluid separated by a semipermeable barrier necessarily tend to exchange constitutents and, if otherwise undisturbed, eventually reach equilibrium. Thus there has never been any question of affirming or denying the participation of these thermodynamic forces in the formation of the intraocular fluid. The problem has been in the first place to discover what precisely is the composition that one should expect to find in the aqueous if this fluid were in fact in equilibrium with the blood across a barrier impermeable only to the plasma proteins. A second question follows as to how far the actual composition of the aqueous fluid agrees with that predicted. Finally, the effort has been made to solve the question as to what these findings imply as to the mechanism of maintaining the normal intraocular pressure and as to the possible cause or causes of glaucoma. These three logically independent but historically intertwined questions have now been pursued to a fairly complete clarification. The path toward that clarification has been painfully slow. Most of the difficulties and errors appear to have arisen from an inadequately detailed application of physicochemical theory. By way of illustrating these difficulties, the story of the aqueous chloride may be considered.

THE CHLORIDE CONTENT OF THE AQUEOUS

In the first steps toward these studies it was naively assumed that the composition of an ultrafiltrate of the blood plasma should be identical with that of the nonprotein fraction of the blood plasma. It was found that the chloride content of the aqueous was appreciably higher than that of the blood. The same problem existed in respect to many other body fluids and forced Jacques Loeb,[3] Van Slyke and his co-workers,[4] Henderson [5] and Robert Loeb and his co-workers [6] into a thorough study of the thermodynamic problem involved. They found that an English

3. Loeb, J.: Membrane Equilibria in Relation to Protein-Containing Fluids, J. Gen. Physiol. **3**:557 and 667, 1920; **4**:351 and 463, 1921.

4. Van Slyke, D. D., and others: Studies of Gas and Electrolyte Equilibria in the Blood, J. Biol. Chem. **54**:121, 149, 481 and 507, 1922. Van Slyke, D. D.; Wu, H., and McLean, F. C.: Studies of Gas and Electrolyte Equilibria in the Blood: V. Factors Controlling Electrolyte and Water Distribution in the Blood, ibid. **56**:765, 1923. Van Slyke, D. D.: Factors Affecting the Distribution of Water, Electrolytes and Gases in the Animal Body, Philadelphia, J. B. Lippincott Company, 1926.

5. Henderson, L. J.: Blood as a Physico-Chemical System, J. Biol. Chem. **46**:411, 1921.

6. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, J. Gen. Physiol. **4**:591, 1922.

chemist, Donnan,[7] had in 1911 formulated the mathematical theory applicable to this problem. They applied Donnan's theory to the complex body fluids and fittingly attached Donnan's name to the equilibria among these biologic fluids.

The problem which Donnan had studied concerned the equilibrium between two fluids separated by a semipermeable membrane when one of these fluids contained a colloidal component to which the barrier is impermeable. In particular, he studied the effect on the equilibrium resulting from the acidic or basic characteristics of the nondiffusible components. Suppose, for instance, that the nondiffusible component is an acid which is present in neutral solution as the salt of a diffusible base along with other diffusible salts. Since the total amount of acid must equal the total amount of base, it follows that the total diffusible acid is less than the total diffusible base. Since acid and base must balance also in the dialysate, it follows that the concentrations of the diffusible ions in the dialysate cannot be identical with those in the mother liquor. If the diffusible ions are all monovalent, Donnan showed that the concentration (more specifically the activity) of both acids and bases in the dialysate was equal to the geometric mean of the activities of the same ions in the mother liquor. Thus, if the base-binding power of the nondiffusible acid accounts for 10 per cent of the total base present, then the diffusible base in the dialysate will be approximately 5 per cent less and the diffusible acid in the dialysate will be approximately 5 per cent more than in the mother liquor. The factor by which these activity ratios differ from unity is called the Donnan factor.[8] The base-binding power of the plasma proteins varies in different persons and in different species, and there are corresponding variations in the Donnan factor. In rabbits and horses, animals with a relatively low concentration of plasma proteins, the Donnan factor is approximately 96 to 97 per cent. In man, values of 93 to 96 per cent have been obtained; in dogs, 92 to 94 per cent.

In the first attempt at the systematic application of Donnan's theory, Duke-Elder[9] omitted computation of the base-binding capacity of the plasma proteins and assumed that Donnan's requirements were satisfied when he found the plasma : aqueous ratio for chloride was equal to the aqueous : plasma ratio for sodium. Both these ratios differed from unity by approximately 20 per cent, roughly four times as much as was to be expected in the species (horses) studied. It is to the credit of

7. Donnan, F. G.: Theory of Membrane Equilibria, Ztschr. f. Elektrochem. **17**:572, 1911.

8. This applies to monovalent ions. For divalent ions, the activity ratio is the square of the Donnan factor; for trivalent ions, the cube.

9. Duke-Elder, W. S.: The Nature of the Intra-Ocular Fluids, Brit. J. Ophth., 1927, supp. 3.

Duke-Elder that he and his associates were the first to correct this error.[10] Moreover, as he pointed out, his first experiments were open to criticism because pooled samples of aqueous and blood from many different animals were used for analysis. Repeating the experiments with analysis of blood and aqueous withdrawn simultaneously from the same animal, he obtained results that checked satisfactorily with Donnan's theory. These results are in accord with those of other workers in this field,[11] though there has been a general tendency to find the aqueous chloride slightly in excess of the calculated equilibrium.

More recently, Duke-Elder and his co-workers[12] have returned to the same problem, since they found that osmotic changes in the blood due to excitement and muscular activity during ether anesthesia might have disturbed their earlier findings. In these latest most refined studies, using aqueous obtained after local anesthetization of the eye, they find not only for chloride but also for sodium and total crystalloid an appreciable excess (2 to 4 per cent) over that expected at equilibrium. These deviations appear to be well beyond any experimental error and force one to conclude that the aqueous deviates in these respects from a dialysate of the blood plasma. However, the possibilities of a simple physical or physicochemical explanation for these discrepancies have not been exhausted. The blood is not the only fluid with which the aqueous is in semipermeable communication. Through the cornea an osmotic interchange with the tears is not impossible. It is true that any exchange across this relatively thick barrier must be much slower than that across the capillary walls, but Ridley[13] has shown that measurable volumes of water may be forced through the cornea under moderate pressure. Goldmann and Rabinowitz[14] have presented evidence that in rats, if winking is avoided, the salt concentration of the aqueous rises 10 per cent in ten to fifteen minutes. Even with winking an evaporation of the tears takes place, so that the film of fluid on the surface of the cornea is markedly hypertonic. Moreover, it has been

10. Davson, H.; Duke-Elder, W. S., and Benham, G. H.: Ionic Equilibrium Between Aqueous Humor and Blood Plasma in Cats, Biochem. J. **30**:773, 1936.

11. Krause, A.: Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934.

12. Benham, G. H.; Duke-Elder, W. S., and Hodgson, T. H.: Osmotic Pressure of Aqueous Humour in Normal and Glaucomatous Eyes, J. Physiol. **92**:355, 1938. Davson, H.: Sodium Content of Blood Serum and Aqueous Humour, ibid. **96**:194, 1938. Hodgson, T. H.: Chlorid Content of Blood Serum and Aqueous Humour, ibid. **94**:118, 1938.

13. Ridley, F.: An Experimental Investigation into the Intra-Ocular Pressure and Aqueous Humour, Tr. Ophth. Soc. U. Kingdom **50**:268, 1930; Brit. J. Exper. Path. **11**:217, 1930.

14. Goldmann, H., and Rabinowitz, G.: Production of Slat Cataract in Young Rats, Klin. Monatsbl. f. Augenh. **81**:771, 1928.

shown [15] that oxygen and carbon dioxide penetrate the cornea with sufficient velocity to affect appreciably the partial pressure of these gases in the aqueous and, furthermore, that the rate of diffusion of gas through the cornea is markedly influenced by local anesthesia.[16]

THE AQUEOUS AS A DIALYSATE

The story of the aqueous chlorides has been chosen to illustrate the slow development of knowledge regarding possible physicochemical equilibria in the eye. To return to the three questions which these investigations were intended to illuminate, the first question as to what is the expected chloride content of the aqueous on the assumption of thermodynamic equilibrium has been answered with sufficient accuracy. The second question as to whether the actual chloride content agrees with that expected can also be answered. There is approximate agreement, but a small discrepancy remains. It seems likely that this small discrepancy may be accounted for by evaporation through the cornea. One finally comes to the third question: What do these findings imply in respect to the nature of the mechanisms normally controlling the intraocular pressure and in respect to the possible causes of glaucoma?

The agreement between chloride found in the aqueous and chloride expected on the basis of thermodynamic theory is approximate and conditional. It is dependent on some as yet unproved assumptions regarding water losses through the cornea. Moreover, it will be shown subsequently that for certain other substances discrepancies of much greater magnitude exist between concentrations found in the aqueous and those expected in the dialysate of blood plasma. For the sake of the argument, however, these discrepancies may for the moment be waved aside and it may be assumed that chemical analyses of the aqueous had revealed its composition to be exactly that of a dialysate of the blood plasma. What would this imply in respect to intraocular fluid exchange?

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15. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: VI. Intra-Ocular Gas Exchange, Arch. Ophth. **17**:477 (March) 1937.

16. The amount of water loss through the cornea required to maintain the increased crystalloid concentration of the aqueous may be estimated as follows: According to Duke-Elder and his co-workers, the aqueous is hypertonic by 3 to 4 per cent when compared with the blood. According to the data of Kronfeld (Verhandl. d. deutsch. ophth. Gesellsch. **49**:296, 1932), as analyzed by Friedenwald and Pierce,[24] an imbalance in crystalloid content between blood and aqueous disappears at the rate of 1 to 2 per cent per minute (dextrose, 1 per cent; iodide, 2 per cent). The volume of the aqueous in dog's eyes is 500 cu. mm. Hence a water loss of $0.04 \times 0.02 \times 500$ cu. mm. per minute, that is, 0.4 cu. mm. per minute, would suffice to keep the aqueous concentration up to the level found. Spread over the cornea, this amounts to a film only 3 microns thick. Water losses at this rate seem not at all unreasonable, especially if the permeability of the cornea is increased by local anesthesia.

There are three possibilities in respect to fluid exchange: (*a*) There may be no exchange whatever; (*b*) there may be a general equilibrium between blood and aqueous on which is superimposed a continuous metabolic exchange, a process by which the aqueous while not circulating is everywhere continuously renewed, and (*c*) there may be superimposed on this metabolic steady exchange a general trend for fluid to enter the ocular cavity mainly from certain capillary beds and to leave the ocular cavity mainly through certain other vascular beds, thus producing a through and through circulation. The first possibility may be ruled out immediately. If fluid is withdrawn from the eye it is promptly replenished. The blood-aqueous barrier is not impermeable to water. A decision between the second and the third possibility is not merely of academic interest, since the question of the possible existence of obstructive types of glaucoma is involved in the answer.

The argument that because the aqueous resembles in composition a dialysate of the blood plasma it is stagnant lacks necessary rigor. In order that such an argument might be valid, it would be necessary to assume that the existence of a through and through circulation is incompatible with such chemical constitution. This assumption tacitly underlies the large body of literature in which chemical evidence is adduced to deny the existence of a through and through circulation. This assumption has been shown to be untenable both by argument and by experiment. The argument has been stated as follows:[17] If it is assumed that an ultrafiltrate differs in chemically recognizable features from a dialysate, this must be because some components of the fluid are relatively retarded on filtration, so that the concentration of these retarded components would be lower in an ultrafiltrate than in a dialysate. However, if there is a through and through circulation of the aqueous, the fluid must pass through two barriers, one on entering and the other on leaving the eye. Components which are retarded on entrance may be retarded also on exit. Thus two filtrations in opposite directions cancel each other. Hence no chemical differences are to be expected between a stagnant and a doubly filtered aqueous.

Flexner,[18] confronted by similar questions in respect to the formation of the spinal fluid, proceeded to measure the effect of various filtration pressures on the composition of ultrafiltrates produced in vitro from protein-containing fluids. He found that the intermicellar fluid in protein solutions has the composition of the dialysate, and hence that ultrafiltrates differ from dialysates only in the same way that ultrafiltrates

17. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: I. Rate of Flow, Arch. Ophth. **7**:538 (April) 1932.

18. Flexner, L.: Thermodynamic Analysis of Ultrafiltration, J. Biol. Chem. **121**:615, 1937.

of nonprotein-containing fluids differ from their mother liquors. Hence filtrations produced by small pressures such as are operative within the blood vessels would not produce measurable deviations in the composition of body fluids. It follows that one is unable by chemical analysis to distinguish between a stagnant "dialysate" aqueous and a mobile doubly filtered aqueous.

THE AQUEOUS AS A SECRETION

For the purposes of the argument just completed, it has been assumed that the composition of the aqueous did not differ from that of a dialysate. In respect to inorganic electrolytes, as has been pointed out, an approximate agreement exists. There are, however, some other components present in the aqueous at concentrations which deviate so far from equilibrium that no stretching of the dialysate hypothesis is able to cover them. Two of these, ascorbic acid and hyaluronic acid, deserve special discussion. Ascorbic acid (vitamin C) has been found present in the aqueous in a concentration at least ten times as high as its concentration in the blood. Nevertheless, as Goldmann and Buschke [19] have shown, the aqueous concentration of ascorbic acid rises and falls with that in the blood. Hence the ascorbic acid in the aqueous is derived from that in the blood. It appears to be present in the aqueous in freely diffusible form. It follows that energy must be expended to produce this local concentration of ascorbic acid.

The vitreous fluid contains a mucoid which has been identified by Meyer [20] and called hyaluronic acid. Meyer found that hyaluronic acid is present in the aqueous in appreciable concentration but is not demonstrably present in the blood. There is, therefore, excellent reason to believe that this substance is synthesized locally within the eye.[21] By no stretch of the imagination can the intraocular accumulation of ascorbic and hyaluronic acids be accounted for as a manifestation of thermodynamic equilibrium. It follows that the aqueous is in some sense a "secretion," but it is important not to be misled by the vagueness of words. Certain chemical components have been shown to be "secreted"

19. Goldmann, H., and Buschke, W.: Blood-Aqueous Barrier and Vitamin C, Arch. f. Augenh. **109**:314, 1935.

20. Meyer, K.: Nature of the Ocular Fluids: Hexosamine Content, Am. J. Ophth. **21**:1083, 1938.

21. The lens consumes dextrose and produces lactic acid. Hence it is to be expected that the dextrose concentration in the aqueous would be less and the lactic acid concentration greater than in the blood. Both these conclusions have been confirmed. The deficit in aqueous dextrose currently reported is small (10 to 20 per cent). It seems likely that the aqueous dextrose is overestimated and its local deficit underestimated, due to interfering products derived from ascorbic and hyaluronic acids.

into the ocular fluid. It does not follow, however, that water is secreted into or out of the eye. Joint fluid, for example, contains mucins which are synthesized locally, but it does not follow that there is a secretion of fluid into or out of the joint cavity. Much of the confusion as to what these chemical findings imply in respect to the movement of intraocular fluid can be removed by a more detailed analysis of what is meant by secretion.

The term secretion is frequently used to refer to two distinct phenomena. On the one hand, it designates the process of manufacture of certain chemical substances which are elaborated by certain organs. In this sense, insulin, bile pigments and joint mucin are "secretions" of the pancreas, liver and synovial tissues, respectively. On the other hand, the word is used to describe the transfer of water or other substances across a tissue barrier at the expense of cellular energy. Thus in the "secretion" of gastric juice, water, chloride ions and similar substances are transferred from the blood to the ducts of the gastric glands. Gastric juice and bile do not differ markedly from blood in total osmotic pressure. Nevertheless, they are secretions in the second as well as in the first sense of the work. Synovial fluid contains mucin, but there is no evidence that the fluid is secreted into the joint.

The argument thus outlined may be summarized in the flat statement that the study of the composition of the intraocular fluid gives no knowledge of where or how water enters and leaves the eye. It is not to be inferred, however, that such chemical studies are irrelevant to the problem of intraocular water balance. Such chemical studies reveal new facts that need to be explained in terms of fluid movement. Thus, to take an example from the preceding discussion, the hypertonicity of the aqueous suggests that there may be water losses through the cornea. Similarly, the fact that the aqueous is nearly in thermodynamic equilibrium with the blood in respect to some components and very far from equilibrium in respect to others suggests that the blood-aqueous barrier may be structurally and functionally complex.

LOCAL MECHANISMS FOR THE CONTROL OF INTRAOCULAR PRESSURE

The problem of glaucoma is essentially the problem of the transfer of fluid into and out of the eye. Since the study of the composition of the intraocular fluid gives no knowledge of how the water enters or leaves the ocular cavity, it was necessary to find some other approach to the problem of intraocular fluid exchange. The first question to be asked was: Are there local mechanisms for the control of the intraocular pressure? The fact that the intraocular pressure can be influenced by the local application of drugs shows that such mechanisms exist. The fact that reactive hypotension and hypertension can be elicited by the proper stimuli shows that the reflex control of these mechanisms can

be activated locally. Further evidence as to the nature of these mechanisms has been gained on the one hand from studies regarding the stability of the intraocular pressure when subjected to various disturbing forces and on the other hand from direct measurements of the rates of inflow and outflow of intraocular fluid.

If it is assumed that no local regulating mechanisms exist, then changes in blood pressure or in the osmotic pressure difference between blood and aqueous should produce corresponding changes in intraocular pressure. Thus, if the intraocular pressure is equal to the intraocular capillary pressure minus the blood-aqueous osmotic pressure difference, then an increase in the protein osmotic pressure of the blood should be associated with a fall of intraocular pressure. Robertson [22] has recently tested this conclusion by measuring the intraocular pressure of patients suffering from nephrosis, a condition in which the protein osmotic pressure of the blood is extremely low, resulting in generalized edema. The intraocular pressure was found to be normal, not elevated. Recovery occurs in these cases with a rapid rise in protein osmotic pressure of the blood and disappearance of the edema. Robertson found no fall in intraocular pressure during recovery.

Similar questions arise in respect to cardiac decompensation. With increased venous blood pressure in these cases, tissue edema develops and also increased intracranial pressure. Spinal fluid pressures of 500 mm. of water are not at all uncommon in these cases. Detailed clinical studies with respect to this problem are not available, but it is evident from ordinary clinical experience that any effect of cardiac decompensation on intraocular pressure must be small in comparison with the effect on intracranial pressure.

Sudden changes in arterial blood pressure are well known to have an effect on the intraocular pressure; indeed, the pulse beat can be recorded directly from the eye, but the effect of sustained changes in arterial blood pressure is not a sustained change in intraocular pressure. It is evident that mechanisms of pressure control exist in the eye which are capable of compensating for changes in arterial or venous blood pressure and for changes in the protein osmotic pressure of the blood.

It might be thought that the small effect of changes in arterial and venous blood pressures on the intraocular pressure are to be attributed to the relative stability of the capillary blood pressure. In respect to arterial pressure, this may in part be true, but the marked effect of changes in venous pressure on intracranial pressure shows that the intracranial capillaries readily respond to this force. More directly relevant data are, however, available. When the iris is inflamed, its congested

22. Robertson, J. D.: Intra-Ocular Pressure in Nephrotic Oedema, Lancet **1**: 1435, 1938; Brit. J. Ophth. **23**:106, 1939.

capillaries must be sustaining an abnormally high pressure. Furthermore, since their permeability rises in the inflammatory reaction (edema and exudation are universal accompaniments of inflammation), serum proteins appear in the intraocular fluid, and the protein osmotic pressure difference between blood and aqueous is diminished. Both these factors should tend to increase the rate of fluid flow from iris capillaries to intraocular cavity. That this can lead in some instances to an increase in intraocular pressure is obvious. It is all the more remarkable that normal or subnormal intraocular pressures occur in many cases of acute iritis. It is evident that within limits and under some circumstances normal intraocular pressure can be maintained in spite of increased pressure in some intraocular capillaries, increased rate of filtration of fluid into the eye and decreased protein osmotic pressure difference between blood and aqueous.

In summary, the clinical and experimental evidence on the stability of the intraocular pressure in the face of various stresses indicates that the intraocular fluid exchange is governed by regulating mechanisms capable of compensating for and damping the effects of changes in arterial, venous and capillary blood pressure and changes in the colloid osmotic pressure difference between blood and aqueous. The nature of this regulating mechanism remains obscure, but there is ground for believing that the cause of some forms of glaucoma is a derangement of this local mechanism rather than in a derangement of the general water balance of the whole body. In fact, only the epidemic form of glaucoma associated with epidemic dropsy bears any earmarks of a general disturbance in water balance, and even in regard to this form it is pertinent to inquire why the compensating mechanism which operates so successfully in nephrosis fails to operate in epidemic dropsy.

Intuitions that a local regulating mechanism may be out of balance have, in fact, affected the clinical points of view regarding glaucoma. Many of the so-called "provocative tests" are based on an effort to strain some aspect of the regulating mechanism and hence reveal its defect. Local therapy either with myotics or with epinephrine presupposes the existence of local cholinergic or adrenergic mechanisms capable of influencing intraocular pressure. Suppositions of the same general character lie behind Hamburger's [23] obscure assertions that glaucoma and inflammation are antagonists.

ROLE OF THE IRIS

The existence of local mechanisms for the equilibration of intraocular pressure entails no denial of the operation of thermodynamic forces across the blood-aqueous barrier. All that is implied is that the blood-

23. Hamburger, C.: Acute Glaucoma and Acute Inflammation, Klin. Monatsbl. f. Augenh. **89**:366, 1932.

aqueous barrier is not necessarily uniform, or inert or unchanging with time. The crux of the problem of glaucoma lies in the need to unravel the complexities, activities and variations of the various portions of this barrier, and a first step consists in discovering that under appropriate conditions certain portions of the blood-aqueous barrier do, in fact, behave as simple, inert, unvarying semipermeable membranes. Thus Friedenwald and Pierce [24] showed that substances can be found which, when injected into the anterior chamber, are absorbed from the aqueous at a rate proportional to their concentration. The coefficient of absorption is a linear function of the area of the iris. Kronfeld [25] has shown that for one crystalloid (dextrose) which obeys this logarithmic law of approach to equilibrium the coefficient of diffusion from blood to aqueous and from aqueous to blood are equal. Similar equality in the diffusion rate of oxygen into and out of the aqueous was found by Friedenwald and Pierce [15] provided diffusion of gas through the cornea was excluded. There is thus strong evidence that under certain conditions the iris presents a simple inert semipermeable barrier between blood and aqueous. Disturbances in crystalloid concentration between blood and aqueous tend to become equilibrated across the iris. How important this equilibration is cannot be judged at present, for this effect can be measured only if experimental animals with aniridia and with eyes otherwise normal can be obtained. Surgical production of aniridia in experimental animals has up to now been accompanied by such severe damage as to leave the eyes unfit for further experimentation.

Even the iris does not always present the attributes of an inert semipermeable membrane. Under vasomotor influences, large changes in permeability and in capillary pressure may take place. Toward colloids, both foreign and native, the iris endothelium is actively phagocytic.[26] These substances, therefore, are "secreted" out of the anterior chamber, since cellular activity is utilized in removing them from the aqueous.

The behavior of the iris toward crystalloids and colloids does not enable one to infer with certainty regarding its behavior toward water. At best one can only conclude that there is at present no reason to believe that the normal iris behaves otherwise than as an inert semipermeable membrane toward water. Since normal intraocular pressure exists in many cases of aniridia, the net contribution of the iris to the intraocular water balance is probably small, and regulating mechanisms which control the intraocular pressure must exist outside of the iris.

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24. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: III. Reabsorption of Crystalloids, Arch. Ophth. **10**:449 (Oct.) 1933.

25. Kronfeld, P.: Absorption from Anterior Chamber, Verhandl. d. deutsch. ophth. Gesellsch. **49**:296, 1932.

26. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: IV. Reabsorption of Colloids, Arch. Ophth. **14**:599 (Oct.) 1935.

SOURCE AND OUTFLOW OF THE AQUEOUS

Appreciable movements of water can occur in the eye. Thus if 0.1 cc. is withdrawn from the anterior chamber of a dog or rabbit, the intraocular pressure falls 10 to 15 mm. of mercury but returns to normal in five to twenty minutes. Similarly, if 0.1 cc. is injected into the eye, the pressure rises but returns to normal within one-half hour. There is little difficulty in specifying the location of the chief inflow and outflow portals for the intraocular fluid. If the intraocular pressure is raised, fluid is rapidly reabsorbed from the eye. It can be shown that most of this reabsorption occurs in front of the pupil.[27] In dogs, rates of reabsorption of 10 cu. mm. per minute can often be obtained with pressures not more than 10 to 15 mm. of mercury above normal. If this much fluid were leaking through the cornea, it could readily be seen. Hence the reabsorption must be through Schlemm's canal and the iris. On the other hand, if fluid is withdrawn from the anterior chamber, that chamber becomes shallower, but if fluid is withdrawn from the vitreous, the anterior chamber does not gain in depth. Thus one can be assured that the chief source of fluid replacement is behind the pupil. Edema of the retina occurs in ocular hypotension, but it develops slowly and is not apparent in the few minutes required to replenish the loss of 0.1 cc. of fluid. Hence the source of fluid replacement must be the ciliary body.

With the demonstration that fluid enters the eye mainly by way of the posterior chamber and leaves mainly by way of the anterior chamber, the question of a through and through circulation takes on a new light. If the intraocular pressure is lowered even slightly, some fluid enters from the ciliary body. If the intraocular pressure is raised even slightly, some fluid leaves the anterior chamber. But the intraocular pressure is normally subject to a continuous cycle of variations impressed on it by pulse, respiration, extraocular movements and pressure of the lids. Hence it is clear that a through and through circulation exists. The only questions that remain are whether this flow is continuous or intermittent and what is the volume of the normal circulation. The first question, whether the flow is continuous or intermittent, is largely academic and cannot be answered until the mechanisms of formation and reabsorption are fully understood. In any case, the possibility of obstructive forms of glaucoma is reestablished. The second question as to the volume of the normal circulation has been studied by obstructing the outflow and then measuring the rate of formation at normal pressure.[17] In this way estimates have been obtained of a rate of flow of 1 to 2 cu. mm. per minute in man and dog and of one-fifth this amount in the rabbit.

27. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: II. Mechanism of Reabsorption, Arch. Ophth. **8**:9 (July) 1932.

Thus one is returned to the problem as Leber [1] left it. But, whereas Leber could well be satisfied in having found the chief source and chief outlet of the intraocular fluid, thus laying a firm foundation for the understanding of the obstructive types of glaucoma, present day investigators must pursue the problem further to a full understanding of the mechanisms of inflow and outflow. These questions are still far from answered, but certain avenues of approach to the problems have already been opened.

MECHANISM OF REABSORPTION OF THE AQUEOUS

The most important guide toward an understanding of the mode of action of the reabsorptive mechanism is the fact that the rate of reabsorption of fluid becomes more rapid when the anterior ocular vessels are congested.[27] Since the effect of congestion of the iris vessels must be to promote the transfer of fluid into the eye, and since, as noted before, the hyperemic increase in absorption occurs even when serum is exuding from the iris, the hyperemic increase in absorption must be attributed to Schlemm's canal. By what sort of a mechanism can the canal be supposed to increase in absorptive capacity when the vascular bed with which it is connected is congested?

A hypothesis as to a possible mechanism of operation of Schlemm's canal which would satisfy the requirements has been suggested by Friedenwald.[28] It is argued that, other things being equal, the rate of fluid absorption by the canal will vary with the concentration of plasma proteins in the canal. If plasma enters the canal at an increased rate when the anterior ocular vessels are congested, the absorptive efficiency of the canal would be increased. In order that this should be possible, there must be arterial as well as venous connections of the canal. Such arterial connections were, therefore, sought for and found. In order further to substantiate this hypothesis, it would be necessary to demonstrate that some blood is normally present in the canal and that the amount of blood increases under conditions under which the rate of absorption of fluid increases.

This has now been accomplished by Scholz and Friedenwald.[29] In order to avoid the displacement of fluid from the canal during enucleation and fixation, these investigators used liquid air to freeze the anterior segment of the eye of experimental animals in situ, under anesthesia. They removed the anterior segment in a solid state and allowed it to thaw in fixative solutions. Since there were no pressure differences in the melted tissues, fixation was achieved without displacement of fluid

28. Friedenwald, J. S.: Circulation of the Aqueous: V. Mechanism of Schlemm's Canal, Arch. Ophth. **16**:65 (July) 1936.

29. Unpublished data.

from the canal. It was found that blood cells and plasma were present in the canal in low concentration if the eye had been undisturbed before freezing, but if a dilute solution of ammonia was instilled in the conjunctiva, producing hypotension and, as previously demonstrated, increased rate of absorption of fluid, the canal was found filled with blood. It is therefore permissible to postulate that variations in the rate of reabsorption of aqueous are dependent on variations in the concentration of plasma within the canal and that the control of the rate of reabsorption is vested, at least in part, in the vasomotor control of the afferent arterioles.

There is no contradiction between the assertion that only small transfers of water take place across the iris barrier with moderate changes in hydrostatic and protein osmotic pressure within the capillaries and the hypothesis of large transfers of water into Schlemm's canal under the influence of similar hydrostatic and osmotic forces. The easy penetration of dyes into the canal is evidence of high permeability of its wall. Nor is there any conflict arising out of the apparent small part which the canal plays in crystalloid exchange. In respect to crystalloids, the canal need come into equilibrium only with that portion of the aqueous which is trapped in the spaces of the sclerocorneal trabeculae. Thus one would expect the canal to absorb crystalloids approximately in proportion to its absorption of water.

The possible mode of operation of Schlemm's canal as outlined is presented not as a final theory but as a working hypothesis which can be correlated with the known clinical and experimental findings and is free from any internal contradictions. The hypothesis has already led to the discovery of the arterial connections of the canal and to at least one vasomotor reflex which leads to hyperemia of the canal. Such vasomotor reflexes merit more extended study.

MECHANISM OF SECRETION OF AQUEOUS

Studies on the mechanism of fluid transfer in the ciliary processes by Friedenwald and Stiehler [30] have revealed that they are secretory organs of considerable complexity. It has been found that the epithelium and the stroma of the ciliary processes possess different respiratory enzymes, as a consequence of which the epithelium has greater oxidizing power and the stroma greater reducing power. These two tissues are separated by a membrane or barrier which is capable of reversible oxidation and reduction and hence acts as a mediator facilitating the oxidation-reduction interchange between the two tissues. Such a chemical

30. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

interaction necessarily produces an electric current in the tissues, and the passage of an electric current through the tissue has been shown to result in a transfer of water.

Present investigations in this field by my co-workers [31] and myself are concerned with the identification of the various chemical components of the tissues that are linked together in the chain of oxidations and reductions through which the oxidases of the epithelium are brought into interaction with the dehydrogenases of the stroma cells. Of particular interest are those components of this redox chain which bridge the extracellular gap across the interstitial tissue of the stroma, for this part of the redox chain is composed of highly reactive substances which do not require the presence of enzymes for their activation. Two such substances, ascorbic acid and glutathione, have already been identified in the tissue, and proof of the role of ascorbic acid in the redox chain has been obtained.[32]

The components of the secretory system so far mentioned do not reveal any mechanism of pharmacologic or neurologic control, but recent experiments have shown that the secretory system in the ciliary body of guinea pigs requires epinephrine or some similar substance for its activation. Thus the ciliary processes in this animal at least fall into the group of adrenergic organs. Whether the normal mode of activation is through local sympathetic nerves or by remote control has not been revealed as yet.

These investigations must be pushed much further before they can be endowed with clinical significance. For the present one can conclude that there are in the eye effector mechanisms by which the rates of formation and of reabsorption are governed and that these effector mechanisms are subject to the control of the vegetative nervous system. If there are neuroeffectors controlling the intraocular pressure, there are probably also neuroreceptors which respond to changes in intraocular pressure and initiate the reflexes that terminate in effector action. Here is a field of investigation as yet almost completely untouched.

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31. Wilhelm Buschke, Harry O. Michel and Heinz Herrman. These studies are supported in part by the John and Mary Markle Foundation.

32. Friedenwald, J. S.; Buschke, W., and Michel, H. O.: Circulation of the Aqueous: VIII. Role of Ascorbic Acid (Vitamin C) in Secretion of Intra-Ocular Fluid, Tr. Am. Ophth. Soc. **37**:310, 1939.

USE OF FLUORESCEIN INTRAVENOUSLY AS AN AID TO OPHTHALMIC DIAGNOSIS AND TREATMENT

H. GIFFORD, M.D.
OMAHA

Ehrlich [1] in 1882 described the formation of a vertical green line in the aqueous after intravenous or oral administration of fluorescein to rabbits. Since then a large amount of experimental work has been carried out, especialy in Germany, in an effort to explain the formation of this line. This has led to the use of fluorescein as an experimental medium for various types of research dealing with the production and circulation of the aqueous and the permeability of the capillaries of the eye. Before extensive clinical use can be made of this method, further experimental work will have to be done. Since fluorescein also appears in the spinal fluid, Bonar and Bailey [2] in 1930 reported its use as a diagnostic test for epidemic cerebrospinal meningitis. It has also been used for clinical and experimental work by urologists because it is excreted rapidly by the kidneys.

Before taking up the intravenous use of fluorescein in ophthalmology, it is necessary to have as clear a picture as possible of its action in the body and a clear idea of the circulation of the aqueous as it is known. This becomes a complex problem that is still open to considerable debate, but certain facts have been pretty well established. The fires are still burning under the arguments as to whether the aqueous is merely a dialysate from the blood or is a true secretory product of the ciliary epithelium. Although the extensive work of Duke-Elder [3] shows by various experimental and theoretic methods that the aqueous is chiefly a simple dialysate from the blood, certain clinical observations are not satisfied (iris bombé). A certain amount of mass movement must be present. The convection movements due to the difference in temperature of the cornea and iris were brought out by Türk.[4] This explains the

1. Ehrlich, P.: Ueber provocirte Fluorescenzerscheinungen am Auge, Deutsche med. Wchnschr. **8**:35-37, 1882.

2. Bonar, B., and Bailey, L. G.: Diagnostic Value of Sodium Fluorescein in Epidemic Cerebrospinal Meningitis, Am. J. Dis. Child. **40**:493-499 (Sept.) 1930.

3. Duke-Elder, W. S.: The Nature of the Intra-Ocular Fluids, Brit. J. Ophth., 1927, supp. 3.

4. Türk, S.: Untersuchen über eine Strömung in der vorderen Augenkammer, Arch. f. Ophth. **64**:482, 1906.

formation of the vertical lines of Ehrlich and Stahli and the deposit of corneal precipitates. Until the recent work of Friedenwald [5] in 1938, any mass movement of fluid through the anterior chamber was thought to be small and influenced, as Duke-Elder stated, by the arterial pulsation and movement of the intraocular and extraocular muscles. Duke-Elder could not find evidence of any work being done by the ciliary epithelium. Friedenwald, however, has always taken the opposite view and in his latest publication gave experimental evidence that the ciliary body does show an irreciprocal permeability to water and certain acid and basic dyes. Water and certain basic dyes are transferred from the stroma to the epithelium, i. e., from the blood to the aqueous, and acid dyes are transferred in the reverse direction.

It is sufficient for this study to know that fluorescein, a diffusible acid dye, does pass from the blood into the aqueous and out again by way of the blood stream. Whether it comes chiefly from the iris or the ciliary body is still uncertain, but the work of Hamburger,[6] Friedenwald and Ulrich [7] would lead me to believe that it comes into the anterior chamber by diffusion through the vessels of the iris, and because it acts as an acid dye it disappears by the way of the ciliary body. When its concentration in the blood is less than in the aqueous, it also disappears by diffusion through the iris vessels and the canal of Schlemm. Yoshida [8] has devised micromethods for quantitative studies of fluorescein. He also proved that the concentration of fluorescein in the aqueous of the normal eye is directly proportional to the concentration of diffusible fluorescein in the blood. About 40 per cent of the injected dye is bound to the blood proteins and is not diffussible. Tutui [9] in 1930 substantiated this finding. Blood containing fluorescein can be dialyzed through a semipermeable membrane, and fluorescein appears in the same proportion as it is found in the aqueous (van Creveld [10]). In rabbits Hertel [11]

5. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous, Arch. Ophth. **20**:761-786 (Nov.) 1938.

6. Hamburger, C.: Ernährung des Auges, Ber. ü. d. Versamml. d. ophth. Gesellsch. **12**:119-131, 1913.

7. Ulrich, R.: Beitrag z. d. Untersuchungen über den Flüssigkeitswechsel im Auge mittelst subcutaner Fluorescein-Injectionen, Arch. f. Augenh. **12**:153-163, 1883.

8. Yoshida, Y.: Ueber Wechselbeziehungen zwischen Blut und Kammerwasser, Arch. f. Augenh. **100-101**:470-479, 1929.

9. Tutui, Y.: Ueber das Vorkommen und die Bildung der Ehrlichschen Linie, Arch. f. Augenh. **103**:580-596, 1930.

10. van Creveld, S.: La tension superficielle de l'humeur aqueuse de l'oeil, Arch. néerl. de physiol. **9**:60-66, 1924.

11. Hertel, E.: Ueber die Bedeutung der Ehrlichschen Fluoreszeinversuche, Arch. f. Augenh. **100-101**:460-469, 1929.

showed that a decrease in the blood protein speeded up the interchange of fluorescein. With an increase in blood protein, the interchange was inhibited. Any increase in capillary permeability was shown to increase the rate of appearance and its concentration in the aqueous. Linksz [12] showed that sympathectomy caused a more rapid appearance of the dye in the eye on the side operated on. Wessely [13] showed that physostigmine salicylate produced a similar effect. This was also confirmed by Ulrich. To state the physiologic action of this dye more concisely, it is nontoxic when injected intravenously or taken orally; it acts as a diffusible acid dye; it is absorbed by the blood protein and other body tissues (skin, conjunctiva and sclera); it is found in the body fluids in direct proportion to its concentration in the blood; it is excreted rapidly by the kidney and other secretory glands (salivary and sweat glands); it appears in the aqueous as a simple dialysate from the blood. Its rate of appearance and concentration in the aqueous depends on at least six factors: (1) the amount of fluorescein injected, (2) the concentration of blood protein, (3) the volume flow of the blood through the eye, (4) the state of capillary permeability in the iris and ciliary body, (5) the size of the anterior chamber and (6) the viscosity or protein content of the aqueous.

Little is known about its appearance in the eyes under pathologic conditions. Thiel [14] in 1925 and Tyson [15] in 1932 made some observations in clinical cases. I could find no others in the German or English literature. Thiel found in glaucoma and other diseased conditions of the eye (iritis) that after large doses of fluorescein by mouth its presence in the aqueous could always be demonstrated. It was not present in the normal eye. This observation is quoted in Head Adler's [16] book on the clinical physiology of the eye and in Duke-Elder's [17] textbook of ophthalmology. Duke-Elder stated further "that one-half hour after the ingestion of 2 grams of fluorescein the aqueous fluoresces if there is inflammation with increased capillary dilation." Tyson gave 2 Gm. of fluorescein internally, which produced staining of the aqueous after three hours in an eye with glaucoma associated with naevus flammeus. The normal eye showed no staining. He believed that this showed an

12. Linksz, A.: Untersuchungen über den Einfluss des Sympathikus auf die Permeabilität der Augenagefässe, Arch. f. Augenh. **104**:264-323, 1931.

13. Wessely, K.: Bemerkungen zu einigen Streitfragen aus der Lehre vom intraokulären Flüssigkeitswechsel, Arch. f. Augenh. **88**:217-252, 1921.

14. Thiel, R.: Ein Beitrag zur Spaltlampenmikroskopie des Auges im ultravioletten Licht, Ztschr. f. Augenh. **58**:86-91, 1925.

15. Tyson, H. H.: Nevus Flammeus of the Face and Globe, Arch. Ophth. **8**:365-371 (Sept.) 1932.

16. Adler, F. H.: Clinical Physiology of the Eye, New York, The Macmillan Company, 1933, p. 322.

17. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1150.

increase in capillary permeability with the formation of the "plasnoid aqueous" causing a diminution of excretion of aqueous with an increase in intraocular tension. A second case is referred to in which the fluorescein test showed similar findings.

When I was a house officer at the Massachusetts Eye and Ear Infirmary, a few clinical tests were made, 20 cc. of a 10 per cent sterile solution of the soluble sodium fluorescein being injected intravenously. With this dose and the aid of the slit lamp, fluorescence of the aqueous was seen in all normal eyes, but its rate of appearance in the anterior chamber was much more rapid in inflamed eyes and in some glaucomatous eyes. The skin and sclera of these persons became intensely jaundiced looking and remained yellow for twenty-four to forty-eight hours. In my recent work, only 10 cc. of a 10 per cent solution [18] has been used, and I find that it is still possible to demonstrate the dye in normal eyes, and the patient's skin has returned to normal color in four to six hours. This increased the amount of available clinical material.

So far I have had no unpleasant experiences in giving this dye. If some of the dye is injected outside the vein, it is easily seen. No slough or inflammation occurs, but the area is a little tender for a few days. The discoloration may last a week. Two young patients became nauseated and vomited. I believe this was due to a psychic factor, but it may have been caused by too rapid injection. The injection should take between two and three minutes, the patient being seated in front of the slit lamp in a position for rapid observation. A narrow beam or pinhole opening is used for examination of the aqueous and vitreous. For hospitalized patients the hand slit lamp made by Bausch and Lomb is equally good. Ordinary oblique illumination can also be used. The time is taken when the injection is finished and again when the first definite greenish tinge is noticed. This end point is sometimes indefinite, but by watching a little longer it finally becomes definite in every case and can be seen grossly as easily as with the aid of the microscope. The time for disappearance is too vague an end point to attempt to determine. The dye is excreted rapidly by the kidneys, the first urine being highly colored. Some color persists for at least twenty-four hours. False tests for sugar will be reported by the laboratory for four to five days. (The fluorescein gives a green color to the Benedict solution.) There is undoubtedly some irritation of the kidney, as slight frequency and burning are complained of occasionally, but in no case has this been severe, and most patients never mention it. Occasional cells may be

18. Soluble sodium fluorescein powder is supplied by the National Analine Company in 25 Gm. bottles. One gram of fluorescein is added to 10 cc. of physiologic solution of sodium chloride and autoclaved fifteen minutes. Material for ten to fifteen injections is made up at one time. A sample is checked for sterility and toxicity by inoculation into a rabbit. This preparation was done by the University of Nebraska College of Medicine, Department of Physiology.

found but no casts or albumin. In severe nephritis this procedure might be contraindicated, but with normal renal function I feel that it is perfectly harmless and in certain cases gives valuable information for diagnosis and treatment.

A definite dosage according to weight was not attempted because of the variable factors of volume flow and blood protein concentration which could not be controlled. The dose of 1 Gm. in 10 cc. physiologic solution of sodium chloride was used in all cases, since this did not discolor the skin too much and has been easy to detect in all cases. The size of the anterior chamber is another uncontrollable variable factor which influences the concentration of the dye and therefore influences the time when the concentration of fluorescein reaches a point at which it becomes visible. Theoretically, the smaller the chamber the more rapidly will the dye become concentrated. The magnitude of this factor has not been determined, but it seems small compared to capillary permeability. The effect of increased protein content in the aqueous has not been definitely shown. Tutui showed in rabbits that it decreased the normal convection movement and therefore delayed the formation of Ehrlich's line, but its higher protein content may also aid in absorbing fluorescein and therefore speed up the concentration of the dye. Since an increased protein content or "plasnoid aqueous" is caused by increased capillary permeability, it would seem that these two factors are parallel in effect, both aiding in increasing the concentration of the dye. The slowing effect of increased viscosity must be very small proportionately. Clinically, cases of iritis substantiate this. This test therefore is not a true test of capillary permeability to fluorescein unless these other factors are controlled. Capillary permeability seems to be the largest factor, and by determining the appearance of fluorescein in the aqueous the test becomes at least a partial measure of this permeability.

The following tabulated case reports give only a rough cross section of the possible application of this procedure, and I hope they will simulate further clinical and experimental investigation.

Data for Normal Eyes

Case No.	Sex	Age, Yr.	Weight, Pounds	Tension	Time of Appearance of Dye, Min.
1	F	63	142	O. S. t.t.l [19]	3
2	F	61	150	O. S. 22	2
3	M	33	166	D. D. t.t.l	3½
				O. S. t.t.l	3½
4	M	20	165	O. S. 19	3½
5	M	9	60	O. S. 17	2

In these eyes the average time for the appearance of fluorescein in the aqueous was about three minutes.

19. t.t.l. means tension was low or normal.

Case of Aniridia

Case No.	Sex	Age, Yr.	Weight, Pounds	Diagnosis	Tension	Time of Appearance of Dye, Min.
1	M	21	165	Aniridia with glaucoma and cataract in each eye; glaucoma controlled with pilocarpine and physostigmine salicylate; zonule intact; no vitreous seen in anterior chamber	O. D. 22 O. S. 25	O. D. 12 O. S. 12

In this case there was only the smallest vestige of iris behind the limbus in each eye, but in spite of this the increased pressure was controlled by pilocarpine. The pressure increased when the administration of drops was stopped for a few days. This case also demonstrates the role of the iris in secreting aqueous. With nearly a complete absence of iris, the time of appearance of fluorescein was delayed to twelve minutes.

In 5 cases of keratoconus in which at least one or more of the characteristic signs were present, the time of the appearance of fluorescein was definitely prolonged over the normal, ranging from eight to fifteen minutes, with an average of twelve minutes. Although the extent of the keratoconus varied from "very slight" to "moderately extreme" in the two eyes of the same person, the time of the appearance of the dye was the same for both eyes. This would seem to rule out an altered secretion of the aqueous as the direct cause of keratoconus, but there may be other factors inherent in the cornea itself which determine which eye will be affected and to what extent. The fact remains that in this group of cases there was a definite increase in the time for the fluorescein to appear that cannot be explained by the differences in body weight or the larger anterior chamber associated with keratoconus (case 8, glaucoma series). The central area of the cornea must certainly derive some of its metabolic needs from the aqueous,[20] and if aqueous secretion is slowed down, as this work would indicate, it is reasonable to say that at least one of the factors in the production of keratoconus is the diminished or altered secretion of the aqueous due to changes in the capillary permeability of the iris and ciliary body. This, of course, suggests the use of parasympathetic-stimulating drugs in the therapy of this condition.

The dye did not appear any more rapidly in the eye into which physostigmine salicylate was injected (case 7). The small pupil made observation difficult, and it is possible that it may have been present sooner. There was only a moderate increase in the time of appearance of the dye in the 2 cases of suspicious keratoconus (6 and 7), and no conclusion can be made from these at this time.

20. Gundersen, T.: Results of Autotransplantation of Cornea into Anterior Chamber, Arch. Ophth. **20**:645-650 (Oct.) 1938.

Cases of Keratoconus

Case No.	Sex	Age, Yr.	Weight, Pounds		Diagnosis	Vision	Time of Appearance of Dye, Min.
1	M	46	190	O. D.:	Keratoconus; stria and superficial opacities	20/70; with contact glass 20/20	14
				O. S.:	More severe keratoconus; stria and superficial opacities; marked thinning crack in Descemet's membrane	20/200	15
2	F	42	204	O. D.:	Keratoconus; secondary glaucoma and bullous keratitis; eye enucleated	.....	..
				O. S.:	Keratoconus; early vertical lines	20/30; with a +1.25 cyl., ax. 10, 20/20	12
3	M	15	105	O. D.:	Keratoconus; no thinning, stria or ring; faint deep opacities	20/30 with a —1.50 cyl., ax. 180	10
				O. S.:	Keratoconus; no thinning or stria, definite ring of pigment; fine superficial opacities	20/100 with a —3.00 sph. ⊃ —8.00 cyl., ax. 45	10
4	F	19	120	O. D.:	Keratoconus; sharp curve; no thinning, stria or ring	20/70 with a —3.00 sph. ⊃ +8.00 cyl., ax. 20; with a contact glass, 20/30	15
				O. S.:	Keratoconus; slight thinning, fine interstitial opacities; definite pigment ring	5/200 with a —2.00 sph. ⊃ ? cyl.; with a contact glass, 20/30	15
5	M	18	102	O. D.:	Keratoconus; opacities in tip; slight thinning; stria; no ring	.....	8
				O. S.:	Keratoconus; fine opacities in tip; slight thinning; stria; no ring	.....	8
6	F	31	130	O. D.:	Keratoconus (?); no thinning, stria, ring or opacities; early	20/20-1 with a —1.50 sph. ⊃ —1.50 cyl., ax. 90	8
				O. S.:	Keratoconus (?); slight thinning; no stria, ring or opacities; irregular central shadows, large cornea and deep anterior chamber; gray hair in one year	20/40 with a —4.50 sph. ⊃ —4.00 cyl., ax. 145; with pinhole, —20/30-1	5
7	F	52	150	O. D.:	Keratoconus (?); no stria; 5 drops of physostigmine salicylate; pupil small	Contact glass of little aid, 20/200; 20/50 with a —1.50 sph. ⊃ —1.50 cyl., ax. 40; unimproved with pinhole	7
				O. S.:	Keratoconus (?); no stria, nuclear sclerosis; central shadow; pupil normal	Contact glass of little aid; 20/100; 20/40 with a +0.00 sph. ⊃ —1.00 cyl., ax. 135; unimproved with pinhole	8

The cases of glaucoma are too few to even attempt to analyze. They simply show a rather wide variation, depending on factors that are not constant. With further study it is hoped that the type of glaucoma due to increased secretion may be separated from the purely obstructive type.

Cases of Glaucoma (Primary)

Case No.	Sex	Age, Yr.	Weight, Pounds	Diagnosis	Tension	Time of Appearance of Dye, Min.
1	F	53	130	Chronic simple glaucoma for one year at least; shallow chambers; no cupping or atrophy in right eye with good visual field; extensive cupping and atrophy in left eye with central visual field only	O. D. 52 O. S. 56	O. D. 2 O. S. 2
2	F	48	140	Chronic simple glaucoma; controlled with pilocarpine 4 times a day since 1934; no change in visual fields or loss of vision; no cupping of disks	O. D. 25 O. S. 28	O. D. 5 O. S. 7
3	M	59	175	Absolute glaucoma in each eye; no perception of light; pupils dilated; corneas steamy; deep cupping; deep anterior chambers; few old synechiae	O. D. 75 O. S. 100	O. D. 7 O. S 6

Cases of Glaucoma (Secondary)

4	M	31	180	Old uveitis, sympathetic (?), in right eye; iridectomy in 1935; no vitreous in anterior chamber	O. D. 60	O. D. 5
5	F	61	150	Cataract operation on left eye in 1936; trephining in 1937; no bleb; vitreous pulled up to wound and trephine opening; controlled with pilocarpine 4 times a day	O. S. 25	O. S. 2
6	F	35	166	Old injury; slightly dislocated lens; slightly tremulous iris; prostigmine administered; pupil small; cornea faintly steamy; vitreous in anterior chamber (?)	O. D. 48	O. D. 7
7	F	70	156	Postoperative cataract; secondary glaucoma; cyclodialysis in 1938; herniation of vitreous into anterior chamber; controlled with pilocarpine 4 times a day Comment: Herniation of vitreous into anterior chamber did not color with fluorescein until 12 minutes	O. S. 30	O. S. 4
8	M	57	152	Aphakia in the right eye; linear extraction 22 years previously; secondary glaucoma; chamber very deep; tremulous iris; cupped and atrophic disk; loss of upper half of visual field; old vascularized corneal scar in left eye; iris adherent to cornea above; faint perception of light temporarily Comment: Vitreous fibers in anterior chamber of right eye did not stain; corneal vessels of left eye looked greenish and cornea around vessels was green	O. D. 29 O. S. 30	O. D. 2 O. S. 4
9	M	9	60	Traumatic dislocation of lens; vitreous herniated into anterior chamber; secondary glaucoma, controlled with pilocarpine Comment: Vitreous did not stain at 15 minutes	O. D. 25	O. D. 1

The dye was used in cases 1 and 2 in an attempt to demonstrate definitely the presence of fluid vitreous in the anterior chamber. These cases, with cases 6 and 7 (secondary glaucoma series), tend to show a slower secretion. There were no clear spaces in the aqueous that represented vitreous. The dye merely diffused slowly and evenly backward

into the vitreous chamber as far as could be seen. Where there was a definite herniation of vitreous with a line of separation at the face of the vitreous (cases 4 and 7, glaucoma series) there was no staining of the vitreous for at least twelve minutes. This gave ample time for the selection of a proper area for a filtering operation that would filter aqueous and not be mixed with vitreous. I feel that this is a valuable procedure in cases of glaucoma following cataract extraction in which the face of the vitreous is often pulled up into the wound. The proper selection of an operative area may determine the success or failure of the operation to relieve tension.

In case 4 the eye was congested and showed a rapid appearance of the dye, as would be expected with increased capillary dilatation. In

Miscellaneous Cases

Case No.	Sex	Age, Yr.	Weight, Pounds	Diagnosis	Comment	Tension	Time of Appearance of Dye, Min.
1	M	16	140	Dislocated lenses; deep chamber; tremulous iris; vitreous in anterior chamber	Fluorescence of vitreous at 25 min.	O. U. 17	O. U. 8
2	M	31	180	Old injury and uveitis; sympathetic ophthalmia (?); dislocated cataractous lens; vitreous in anterior chamber	Fluorescence of vitreous at 15 min.	O. S. 19	O. S. 6
3	F	63	142	Separation of retina ten days after operation; still congested	Retina did not stain	O. D. ?	O. D. 3
4	F	70	156	Postoperative cataract; loss of vitreous; vitreous against posterior cornea; shallow anterior chamber, still congested; no cells in anterior chamber	Vitreous did not stain until 12 min.	O. D. 26	O. D. 1
5	M	20	150	Epithelial cyst in anterior chamber; perforating injury 18 years before; slow healing; incarceration of iris; cyst filled two thirds of anterior chamber, touching back of cornea; vessels in wall of cyst; eye extremely congested	Fluid in cyst showed no color after 20 min.	O. D. 19	O. D. 2

case 3 the eye was also irritated and showed a similar, rapid appearance. The injection was done in this case in an attempt to stain the separated retina. This procedure was suggested by Sormsby,[21] who with Kiton fast green V (40 cc. of a 10 per cent solution) was able to stain the edges of the retinal tear, making the hole more visible. The fluorescein in my case did not show in the retina either because it was not concentrated enough or because it may not be absorbed by nerve tissue.

Case 5 is of interest because it was definitely demonstrated that the fluid in the epithelial cyst was not in free communication with the aqueous. The eye in this case was also congested and showed a rapid appearance of the dye.

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21. Sormsby, A.: Vital Staining of the Retina, Brit. J. Ophth. **23**:20-22, 1939.

SUMMARY AND CONCLUSIONS

The intravenous injection of solution of sodium fluorescein (10 cc. of a 10 per cent solution) is presented as a method of studying the circulation of the aqueous in clinical cases. It has been found to be nontoxic and produces no really unpleasant symptoms in the patient. The time of appearance and its concentration in the aqueous depend chiefly on the state of capillary permeability in the iris and ciliary body. The volume flow of blood, the concentration of blood protein, the size of the anterior chamber and the viscosity of the aqueous appear to be minor factors.

The appearance of fluorescein in normal eyes is easily demonstrated. In the aqueous it appears on the average in about three minutes.

The time of appearance and the concentration of the dye are definitely diminished in keratoconus. This suggests the use of parasympathetic-stimulating drugs in the treatment of this condition. This test may prove valuable in establishing the diagnosis of early keratoconus.

This procedure has definite value in proving the presence and position of vitreous in the anterior chamber. The delayed appearance of fluid may serve as an indication of fluid vitreous in the anterior chamber. It has proved definitely valuable in selecting the site of a filtering operation for glaucoma following cataract extraction.

In the clinical study of the problem of glaucoma, I feel that it may prove valuable in separating the secretory from the purely obstructive type of disease.

The application of this test to general medicine has not yet been investigated, but the possibility of its use in vascular disorder in which capillary permeability is a factor suggests itself in migraine, malignant hypertension and toxemia of pregnancy.

CONVALESCENT BLOOD FOR TREATMENT OF HERPES ZOSTER OPHTHALMICUS

SECOND REPORT

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Five years ago I reported [1] the results obtained by using convalescent blood in the treatment of 10 patients with herpes zoster ophthalmicus. The results were compared with those obtained in a control series of 19 patients not treated by any specific remedy. In both series the eyes were definitely infected with the virus of herpes zoster. Ten other patients were dealt with separately because their eyes never showed any evidence of keratitis or uveitis.

The results obtained from this new treatment were encouraging. Two patients with definite but early ocular involvement were promptly and dramatically cured; 7 others whose eyes were infected, as a general rule for a longer period before treatment was instituted, showed only gradual improvement, but there was no permanent impairment of vision. Only 1 person (10 per cent) lost useful vision. The previously mentioned control series of 19 patients showed the following results: The vision of 11 (or 58 per cent) was reduced below 6/60 and of 2 others down to 6/15. The vision of the remaining 6 patients was normal. Thirty-nine patients in all were mentioned in the first report: Ten were treated, 19 were not treated and 10 were without ocular involvement (table 1). During the past five years, 52 additional patients have come under my observation. Twenty-three of these presented definite evidence of ocular infection. Therefore, of the total of 91 patients, there were 61 (66 per cent) with ocular infections. This percentage corresponds precisely to that given by Hybord,[2] who found 35 ocular infections in a group of 53 patients.

Thirteen additional patients have been treated by immunotransfusion. One of these had active dementia paralytica, which necessitated his

From the Howe Laboratory of Ophthalmology, Harvard University, and the Massachusetts Eye and Ear Infirmary.

1. Gundersen, T.: Convalescent Blood for Herpes Zoster, Tr. Am. Ophth. Soc. **33**:508, 1935.

2. Hybord, A.: Du zona ophthalmique et des lésions oculaires qui s'y rattachent, Thesis, Paris, no. 232, 1872.

TABLE 1.—*Data on Ten Patients with Herpes Zoster Ophthalmicus Treated with Convalescent Blood**

TABLE 1.—*Data on Ten Patients with Herpes Zoster Ophthalmicus Treated with Convalescent Blood* *

Patient; Age, Yr.; Case No.	Date of Onset of Herpes Zoster	Time of Transfusion	Type and Amount of Blood	Donor; Time After Onset of Herpes Zoster	Clinical Severity of Donor's Condition	State of Eye at Time of Transfusion	Clinical Condition of Patient	End Result	Duration of Congestion, Days	Relief from Pain	Duration of Cells in the Aqueous, Days	Duration of Keratitis Punctata, Days
B. C. 53 1	Jan. 5, 1932	January 9 and 10 4th and 5th days	Serum 13 cc.	M. F. 14 mo.	Eruption ++ Pain ++	Vision 6/9 Cornea ++ Uveitis + Congestion +++	Eruption +++ Pain ++ Nasal vesicles present	Vision 6/6 Atrophy of iris +++ Cornea, fine scattered maculas	42	Marked after 24 hr.	150	170
C. F. 56 2	Jan. 28, 1932	April 1 and 8 63d and 70th days	Defibrinated blood 80 cc.	N. K. 12 mo.	Eruption + Pain +	Vision 6/12 Cornea ++ Uveitis +++ Congestion +	Eruption +++ Pain +++ Nasal vesicles present	Vision 6/6+2 Atrophy of iris, slight Cornea, few small faint maculas	90	None	180+	180+
M. P. 64 3	Aug. 15, 1931	April 2 and 8 223d and 229th days	Defibrinated blood 65 cc.	N. K. 12 mo.	Eruption + Pain +	Vision 6/12 Cornea ++ Uveitis ++ Congestion +	Eruption ++ Pain ++ Nasal vesicles present	Vision 6/4.5 Atrophy of iris ++ Cornea, few fine maculas	450+	No pain	450+	450+
A. M. 55 4	May 22, 1932	June 2 11th day	Whole blood 450 cc.	M. H. 5 mo.	Eruption + Pain +	Vision 6/21 Cornea ++ Uveitis +++ Congestion ++	Eruption +++ Pain +++ Nasal vesicles present	Vision 6/6 Atrophy of iris +++ Cornea, few fine scattered maculas	18	Very marked after 48 hr.	28	180
T. M. 63 5	June 25, 1932	June 29 4th day	Whole blood 450 cc.	B. C. 6 mo.	Eruption ++ Pain ++	Vision (?) Cornea ++ Uveitis ++ Congestion ++	Eruption ++ Pain ++++ Nasal vesicles present	Vision 6/9+ Atrophy of iris, none Cornea, clear	8	Marked in 24 hr.	8	Had none
C. W. 38 6	Jan. 27, 1933	February 21 25th day	Whole blood 300 cc.	E. A.M. 27 mo.	Eruption +++ Pain +++	Vision 6/30 Cornea ++ Uveitis +++ Congestion +++	Eruption ++ Pain ++++ Nasal vesicles present	Vision 6/6 Atrophy of iris ++ Cornea, fine scattered maculas	140	Marked in 24 hr.	120	150
W. B. 61 7	April 22, 1933	April 28 6th day	Whole blood 500 cc.	B. C. 15 mo.	Eruption ++ Pain +	Vision 6/12 Cornea ++ Uveitis +++ Congestion +++	Eruption +++ Pain + Nasal vesicles present	Vision 6/6 Atrophy of iris ++ Cornea, few scattered scars	240	Little pain	270+	270+
M. A. 70 8	Oct. 12, 1933	October 18 6th day	.....	M. H. 22 mo.	Eruption + Pain +	Vision 6/60 (estimated) Cornea +++ Uveitis ++++ Congestion ++++	Eruption +++ Pain ++++ Nasal vesicles present	Vision—shadows Atrophy of iris ++ Cornea, large leukoma—perforation	180	Slight relief after every transfusion	Probably 240	240
		October 30 18th day	Whole blood 1,350 cc.	M. H. 22 mo.								
		November 4 23d day	.....	H. M. 5 mo.	Eruption + Pain ++							
M. B. 23 9	July 22, 1934	July 26 4th day	Whole blood 300 cc.	C. C. 18 mo.	Eruption +++ Pain ++++	Vision 6/12 Cornea ++ Uveitis +++ Congestion +++	Eruption ++ Pain ++++ Nasal vesicles present	Vision 6/6 Atrophy of iris, none Cornea, clear	13	Very marked in 20 hr.	13	Had none
A. H. 69 10	Oct. 30, 1934	November 13 13th day	Whole blood 450 cc.	C. C. 23 mo.	Eruption +++ Pain ++++	Vision 6/15 Cornea ++ Uveitis +++ Congestion +++	Eruption ++ Pain ++ Nasal vesicles absent	Vision 6/15 Atrophy of iris + Cornea, moderate scarring Eye congested	92+	Very slight	92+	92+

* In the sixth, seventh, eighth and ninth columns of this table and of table 2, + indicates mild; ++, moderate; +++, severe, and ++++, very severe.

removal to a state hospital. This patient could not be followed and therefore has been excluded from consideration. A detailed analysis of the data for the 12 remaining patients is given in table 2.

For the entire series of patients, now totaling 22, who up to the present time have received herpes zoster convalescent blood and the final outcome of whose condition is known, the following results, as evaluated by visual acuity, have been obtained: Eighteen patients (82 per cent) retained useful vision (better than 6/18) in the affected eye and 4 patients (18 per cent) lost useful vision. These will be considered in detail later.

For comparison, I shall consider the 39 patients whose eyes were affected but who received no specific therapy. Fifteen of these (40 per cent) lost useful vision (below 6/18). In addition, 5 others had seriously impaired vision (between 6/15 and 6/18). If these are included in the group of patients who lost useful vision, the total becomes 20 (or 53 per cent). Therefore, it may be said that if an eye is affected by herpes zoster and no specific remedy is employed, there is between 40 and 53 per cent chance of the patient losing useful vision.

This method of evaluating a form of therapy, namely, by comparing the visual end results for a group of treated patients with those for a control group of untreated patients, is doubtless good, but its accuracy is proportional to the numbers of patients included in the groups. Only when large numbers of patients are dealt with can statistics be conclusive. Many factors make for inaccuracies in this method. For example, any preexisting disease of the eye, such as atrophy of the optic nerve, amblyopia, cataract, glaucoma or central corneal scars, would preclude the possibility of an accurate evaluation by this method.

In view of this possible inaccuracy, I have also used another method of evaluating the effects of the treatment in these cases. According to impressions obtained by the consideration of subsequent factors, I have divided them into the following three groups:

Group A consists of cases in which the natural course of the disease appeared to be favorably affected by the treatment. In these cases no new corneal infiltrates developed, and the ones already present when the transfusion was given showed some absorption; the aqueous cleared, and in most cases there was a lessening in the amount of pain. In this group are placed 12 cases: 5, 9, 11, 12, 13, 15, 17, 18, 19, 20, 21 and 22.

Cases 5 and 9, the first 2 in this group, were cited in detail in my first report. Both patients were treated on the fourth day after vesiculation with large amounts of blood (450 and 300 cc.) from donors who had recovered from herpes zoster six months and eighteen months before. A repetition of the account of the brilliant results attained in these cases is unnecessary.

Nine other cases included in group A are so similar that individual reports of them are unnecessary. They are cases 12, 13, 15, 17, 18, 19, 20, 21 and 22. The important facts regarding them are given in table 2.

It is to be noted that treatment was given as early as the second day and not later than the thirteenth day after vesiculation. In view of the fact that the ocular infection in herpes zoster is rarely coincident with the appearance of vesicles and almost always follows it, even as late as the fourteenth day (in 2 of my cases), the transfusions were all given late as regards the primary infection. The amount of convalescent blood given varied between 250 and 450 cc., which, in view of the results, may now be considered adequate. In other words, even if this amount of blood is given late in reference to the primary cutaneous eruption, good results may be expected if it is given before the ocular infection is well established.

The question as to whether the blood of donors who have had immunotransfusions is equally effective for use as the blood of those who have recovered spontaneously cannot be definitely answered. With 3 exceptions, blood from donors who had recovered spontaneously was given the 12 comprising group A. The donor (B. C.) in case 5 was given a small amount (13 cc.) of herpes zoster convalescent serum with doubtful or little effect. G. S., the donor in case 13, was given 250 cc. of convalescent whole blood, which favorably influenced the course of his disease but did not effect a complete cure. H. V., the donor in case 21, was given 250 cc. of convalescent whole blood from L. O. with little if any effect on her disease. Therefore, all these patients who have been cured by immunotransfusions received blood from donors who either recovered spontaneously from herpes zoster or derived little benefit from the immunotransfusions given them. I have no evidence which shows that passively immunized donors are as good as actively immunized ones, and it is unreasonable to expect that they would be.

I have not yet determined how effective convalescent blood is in preventing ocular infections in herpes zoster. All of these eyes were affected before treatment was instituted. The probability of ocular infection is obviously high—66 per cent of this series of 91 patients and also 66 per cent in Hybord's series of 53 patients. In view of this great chance of ocular involvement and the high incidence of visual loss when no specific remedy is given (40 to 53 per cent), it would seem desirable to employ immunotransfusion immediately after the diagnosis of herpes zoster involving the first division of the trigeminus nerve is made and not to wait until the eye is affected.

The fact that case 11 (G. S.) is included in group A requires explanation. The patient, a relatively young man, aged 30, had a severe

TABLE 2.—*Data on Additional Patients with Herpes Zoster Ophthalmicus Treated with Convalescent Blood*

Patient; Age, Yr.; Case No.	Date of Onset of Herpes Zoster	Time of Transfusion	Type and Amount of Blood	Donor; Time After Onset of Herpes Zoster	Clinical Severity of Donor's Condition	State of Eye at Time of Transfusion	Clinical Condition of Patient	End Result	Duration of Congestion, Days	Relief from Pain	Duration of Cells in the Aqueous, Days	Duration of Keratitis Punctata, Days
G. S. 30 11	May 8, 1935	May 10 3d day	Whole blood 250 cc.	C. C. 28 mo.	Eruption +++ Pain ++++	Vision 6/9 Cornea, clear Uveitis ++ (20 cells per slit lamp beam) Congestion ++	Eruption +++ Pain +++ Nasal vesicles present	Vision 6/18 Atrophy of iris, none Cornea, fascicular keratitis	20	Marked in 4 hr.	50	None
M. W. 35 12	Nov. 7, 1935	November 12 6th day	Whole blood 250 cc.	W. B. 1 mo.	Eruption +++ Pain +++ (herpes zoster costalis)	Vision 6/6 Cornea, clear Uveitis + Congestion +++ (chemosis)	Eruption +++ Pain ++ Nasal vesicles present	Vision 6/6 Iris, normal Cornea, clear	7	Marked in 12 hr.	None	None
C. T. 56 13	Aug. 9 1936	August 21 13th day	Whole blood 300 cc.	G. S. 15 mo.	Eruption +++ Pain +++ (Had transfusion)	Vision 6/12 Cornea + (many infiltrates) Uveitis + (10 cells) Congestion ++	Eruption ++ Pain ++ Nasal vesicles absent	Vision 6/6 Iris, normal Cornea, 1 to 2 fine marginal scars	21	Moderate	4	None
H. V. 50 14	May 15, 1937	May 19 5th day	Whole blood 250 cc.	L. O. 4 mo.	Eruption +++ Pain +++ (Had transfusion)	Vision 6/18 Cornea +++ Uveitis +++ Congestion +++	Eruption +++ Pain +++ Nasal vesicles present	Vision 6/18 Atrophy of iris ++ Cornea +++; scars	730±*	Slight if any	515±	515±
E. P. 71 15	July 15, 1937	July 17 3d day	Whole blood 300 cc.	? 144 mo.	Eruption (?) Pain (?)	Vision 6/18 Cornea ++ (keratitis epithelialis and folds) Uveitis ++ (100 cells) Congestion +++	Eruption +++ Pain ++ Nasal vesicles absent	Vision 6/6 (estimated) Atrophy of iris, none Cornea, clear	14	Little pain	6	None

A. D. 59 16	Sept. 7, 1937	September 26 20th day	Whole blood 350 cc.	L. O. 9 mo.	Eruption +++ Pain +++ (Had trans- fusion)	Vision, fingers at 3 feet Cornea ++++ Uveitis (cells not visible) Congestion ++++	Eruption +++ Pain ++ Nasal vesicles + (tip)	Vision 6/15–2 Atrophy of iris (?) Cornea ++; scars	140	Moder- ate	140	180±
A. P. 75 17	Nov. 7, 1937	November 8 2d day	Whole blood 300 cc.	.....	.....	Vision (?) Cornea + (infil- trates below) Uveitis ++ Congestion ++	Eruption +++ Pain ++ Nasal vesicles present	Vision 6/6 Iris, normal Cornea, clear	28	Moder- ate	28	None
J. F. 55 18	Feb. 18, 1938	February 26 9th day	Whole blood 300 cc.	H. T. 18 mo.	Eruption +++ Pain + (Lost eye)	Vision 6/12 Cornea, negative Uveitis ++++ (fine keratitic pre- cipitates) Congestion ++++	Eruption +++ Pain + Nasal vesicles absent	Vision 6/5 Iris, normal Cornea, clear	25	Little pain	56	120
A. D. 74 19	April 8, 1939	April 15 8th day	Whole blood 300 cc.	P. C. 3 wk.	Eruption +++ Pain +++	Vision 6/15 (cata- ract) Cornea + Uveitis + (10 cells) Congestion +++	Eruption ++ Pain ++ Nasal vesicles + (tip)	Vision 6/15 (cataract) Iris, normal Cornea, clear	25	Moder- ate	25	None
J. A. 24 20	April 12, 1939	April 16 5th day	Whole blood 350 cc.	H. C. 8 mo.	Eruption +++ Pain +++	Vision 6/6 Cornea + Uveitis + (10 cells) Congestion ++	Eruption +++ Pain +++ Midnasal vesicle	Vision 6/6 Iris, normal Cornea, clear	8	Marked in 2 days	13	None
R. F. 52 21	Aug. 7, 1939	August 11 5th day	Whole blood 350 cc.	H. V. 21 mo.	Eruption +++ Pain +++ (Had trans- fusion)	Vision (?) Cornea, clear Uveitis ++ (cells) Congestion +++	Eruption +++ Pain ++ Nasal vesicles + (tip)	Vision 6/6 Iris, normal Cornea, clear	19	Moder- ate	19	None
J. G. 44 22	Aug. 26, 1939	September 1 6th day	Whole blood 450 cc.	C. C. 80 mo.	Eruption +++ Pain ++++	Vision 6/12 Cornea, clear Uveitis + Congestion ++	Eruption +++ Pain ++ Nasal vesicles present	Vision 6/9 Iris, normal Cornea, clear	8	Moder- ate in 2 days	8	None

* ± means approximately.

eruption accompanied by great pain. The eye became infected at practically the same time that vesiculation occurred and showed iritis, as evidenced by spasticity of the pupil and the turbidity of the aqueous. On the third day of the disease a transfusion of 250 cc. of blood was given from a donor who had had herpes zoster twenty-eight months before. Blood from the same donor had presumably affected another patient, M. B. (case 9), favorably ten months previously. The treatment was followed by marked relief from pain in four hours, almost complete whitening of the globe in twenty days and disappearance of cells from the aqueous in fifty days. Then a recurrence of the ocular infection appeared. There developed in the superficial cornea an infiltrate which became heavily vascularized, and a "wandering phlyctenule" ensued. The migration of this infiltrate into the pupillary space resulted in the loss of useful vision. So, in spite of the fact that the infection with herpes zoster showed a definite diminution in its intensity, it was not completely arrested by the transfusion, and a relatively mild recurrence in a particularly vulnerable spot was responsible for the loss of useful vision. I suspect that the quantity of blood given (250 cc.) was not sufficient for this particular patient. The ocular infection showed evidence of almost complete cure in a relatively short time, but a mild recurrence of keratitis in a particularly important place spoiled the visual end result.

Group B consists of the cases in which the effect of treatment was doubtful. In this group are placed 7 cases: 1, 2, 3, 4, 6, 7 and 10. There are a few facts that should be pointed out in regard to this group. The patient in case 1 (B. D.) was given only 13 cc. (total) of serum, but early in the course of the disease—fourth and fifth days. This was less than was used in any case in group A. The patients in cases 2 and 3 (C. F. and M. P.) were likewise given small amounts, 80 cc. and 65 cc. (defibrinated blood), respectively. Furthermore, the treatment was given later than in any case in group A (on the sixty-third and two hundred and twenty-third days). The patients in the remaining 4 cases (4, 6, 7 and 10) were given large transfusions—300 to 500 cc.—a different donor being used for each. In 2 instances the donors had recovered from herpes zoster costalis rather than herpes zoster ophthalmicus. It is unreasonable to suspect that a difference in location of the disease should cause any difference in antibody formation and consequently in the patient's value as a donor. The patients in these 4 cases (A. M., case 4; C. W., case 5; W. B., case 7; A. H., case 10) were given treatment on the eleventh, twenty-fifth, sixth and thirteenth days of their respective diseases. However, in each instance the ocular infection was unusually severe and well established, so that the treatment probably was given after the optimum time.

Group C consists of the remaining 3 cases in which the treatment had no apparent effect on the disease. These cases (8, 14 and 16) are of special interest and the histories follow:

CASE 8 (cited in the first report).—M. A., aged 70, had one of the most severe infections I have ever seen, characterized by extensive vesiculation, intractable pain and systemic signs of herpes zoster encephalitis. The eye was infected almost from the onset of vesiculation. There were marked keratitis, severe iritis with hypopyon, practically complete external ophthalmoplegia and partial paralysis of the facial nerve. Three transfusions of 450 cc. each were given on the sixth, eighteenth and twenty-third days, respectively. Although there was a temporary remission of pain after each treatment, there was little or no improvement in the ocular infection, and perforation of the cornea eventually occurred. The acute phase of the infection subsided in two to three months, but a chronic uveitis of varying intensity persisted, which showed little tendency to subside. Thirteen months after the onset of the herpes, the patient persuaded Dr. Jason Mixter to relieve her pain by section of the gasserian ganglion. The final visual acuity was perception of hand movements only, due to a dense leukoma extending from the lower limbus to the upper pupillary space.

The donor used for the first two transfusions was M. H., who had spontaneously recovered from herpes zoster ophthalmicus twenty-two months before, and for the third transfusion H. M., who had recovered from herpes zoster costalis five months before. Since both donors had recovered from their diseases spontaneously (i. e., without immunotransfusion), it may be assumed that their antibody titer was high. Furthermore, they were both used within two years after their own infections, and in group A I found convalescent blood to be very effective when used within this period. No reason has been found for the complete failure of the treatment of this patient.

CASE 14.—H. V., aged 50, was first seen three days after the outbreak of an extensive herpes zoster ophthalmicus. The patient had some pain, although not severe or prostrating. The eye was congested, and the cornea showed edema and two small infiltrates in the superficial stroma. There was moderate iritis, as evidenced by turbidity of the aqueous. An immunotransfusion was offered, but this was refused by the patient. Posterior pituitary U. S. P. was injected, but without effect. Two days later the pain had increased in severity, as had also the keratitis and iritis, and the vision had decreased to 6/18. The patient now accepted the treatment first proposed, and on the fifth day of the disease 250 cc. of citrated blood was given from donor L. O., who had had herpes zoster ophthalmicus four months before. The immediate effect was not remarkable, although there was some diminution of the pain. Seven days after the transfusion there appeared to be no increase in the involvement of the eye, and the patient was discharged from the hospital. Then came a prolonged period when the eye showed practically all the protein manifestations and complications of ocular herpes zoster. There were remissions and exacerbations of the infection. The infiltrate in the cornea increased to involve most of the lower half, and this area subsequently became vascularized. The acute phase of the iritis subsided but was followed by a prolonged chronic iridocyclitis, characterized by cells in the aqueous, keratitic precipitates and secondary glaucoma. This required repeated paracenteses of the anterior chamber. During the height of the keratitis, the cornea showed edema with many bullae. Several attacks of scleritis followed, which left marks in the sclera not unlike those seen after a healed attack of scleromalacia perforans.

During this prolonged period other treatments were instituted. Ten months after the onset, killed typhoid bacilli were injected intravenously to give the patient an artificial fever and to promote the formation of nonspecific antibodies. No effect was observed. Twenty-three months after the onset the patient was given 350 grains (22.68 Gm.) of sulfanilamide during a period of two weeks. Owing to the development of much nausea and a dermatitis due to sulfanilamide, the administration of the drug had to be discontinued. No immediate improvement in the ocular infection could be seen, but there did follow a gradual improvement, and when the patient was last seen, thirty-one months after the onset, the eye was not congested, there were no cells in the aqueous and the corrected visual acuity was 6/18.

CASE 16.—A. D., aged 59, was not seen until seventeen days after the onset of a severe herpes zoster ophthalmicus. According to the history, the eye became involved at the onset. When the patient was first seen the eye was in a precarious condition. Vision was reduced to counting of fingers at 3 feet (90 cm.), due to tremendous thickening of the cornea and folding of its posterior surface. The cornea was so opaque that the presence of keratitic precipitates or cells in the aqueous could not be determined, although spasticity of the iris gave evidence of an existing iritis. The eye felt softer than its fellow. Two days later, nineteen days after the onset, 350 cc. of citrated blood was transfused from donor L. O., who had had herpes zoster ophthalmicus nine months before. There was considerable improvement in the amount of pain but no noticeable change in the ocular condition, and two days later a broad paracentesis of the anterior chamber was performed. The paracentesis wound was reopened daily for five days, to increase the antibody concentration in the aqueous. Then followed a period of gradual improvement. One month after the onset the cornea had cleared considerably, although there were many scattered deep infiltrates. Five months after the onset the eye was free from congestion, and there were no cells visible in the aqueous. Vision was 6/80.

These 3 patients did have severe and well established ocular infections before treatment was instituted, but no satisfactory reason has been found for the therapeutic failure. A possible reason, however, for failure in cases 14 and 16 is suggested by the fact that both patients were given blood from the same donor L. O.,[3] whose recovery from herpes zoster may have been partially or wholly due to passive immunization.

This brings up the question as to whether or not an infection with varicella confers immunity against herpes zoster. My opinion is that it probably does not, or at least not a complete immunity, for the follow-

3. L. O., a 29 year old man, was seen at the onset of a moderately severe herpes zoster ophthalmicus. The eye became infected four days after vesiculation of the brow and nose. After a fruitless search for a compatible herpes convalescent donor, 500 cc. of blood was given from a person who had had varicella fifteen years before. The result was good but not spectacular. It would fulfil the requirements for inclusion in group B. Relief from pain was marked after two days. Ocular congestion and cells in the aqueous persisted for eight weeks. There were a few small scattered infiltrates in the cornea, which became permanent scars, luckily outside the pupillary area, and vision returned to normal.

ing two reasons: 1. A definite history of varicella has been obtained six times from 25 patients in my series, from whom this information was sought. 2. Varicella convalescent blood did not produce a marked effect on patient L. O.[3]

CONCLUSIONS

A study of additional cases confirms my previous conclusions regarding the value of herpes convalescent blood in the treatment of herpes zoster ophthalmicus. By this method of treatment, if between 250 and 450 cc. of blood is given before ocular infection is well established, good results may be expected.

ANTAGONISM BETWEEN ADRENERGIC DRUGS AND ATROPINE IN THE ISOLATED IRIS DILATOR

PARKER HEATH, M.D.
AND
ERICH SACHS, M.D.
DETROIT

In a reported series[1] of experiments on isolated iris dilator an observation was made that an antagonism existed between atropine and adrenergic drugs on the contracted strip. In other words, the isolated dilator of iris when contracted by a sympathetic or adrenergic drug relaxes to atropine just as the sphincter does when contracted by acetylcholine. This throws doubt on the idea that reactions to sympathetic and parasympathetic drugs predicate a corresponding innervation. Poos[2] from his work on isolated iris muscles favored the idea of a double innervation of the sphincter. He found a depressing effect on the sympathetic side in addition to a contracting, stimulating, parasympathetic action but found no corresponding responses from the dilator, exposed to pilocarpine and choline. Velhagen,[3] on the other hand, demonstrated an unexpected contraction of the dilator in response to acetylcholine, but he rejected the hypothesis of a double innervation of the dilator corresponding to the double innervation of the sphincter. Velhagen interpreted his findings as due to direct action on the muscle, since only high dosage had an effect. This concept is important, because dosages above the physiologic level may cause paradoxic reactions. The study of the kinetics of drug reactions on smooth muscle is complicated by differing response in different species and in different organs of the same subject. Confusion has arisen, consequently, because of doubtful innervations and uncertainties of dosage. Simplification of the problem arises from study of the isolated iris muscle preparation and the use of low concentrations of chemical and biologic stimulators within physio-

From Ophthalmic Research Laboratory, Wayne University.

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2. Poos, F.: Pharmakologische und physiologische Untersuchungen an den isolierten Irismuskeln, Arch. f. exper. Path. u. Pharmakol. **126**:307, 1927.

3. Velhagen, K., Jr.: Zur Frage der vegotropin Substanzen im Auge, Arch. f. Augenh. **105**:573, 1932; Ueber die Wirkungsweise von Cholinkörpern auf die Irismuskeln, ibid. **108**:126, 1933; Neue Untersuchungen über aktive Stoffe im Auge, ibid. **109**:195, 1935.

logic limits. Our problem is to stimulate the dilator physiologically by drugs and in the same preparation similarly apply other drugs, noting either synergism or antagonism. This report verifies and extends the foregoing observation and is part of a series of studies in this field.

METHODS

Methods in these experiments were the same as those described previously, except that the impulse pick-up was not autographic. Further, the muscle strip in the bath did not work against coiled springs. It was impossible to calibrate the

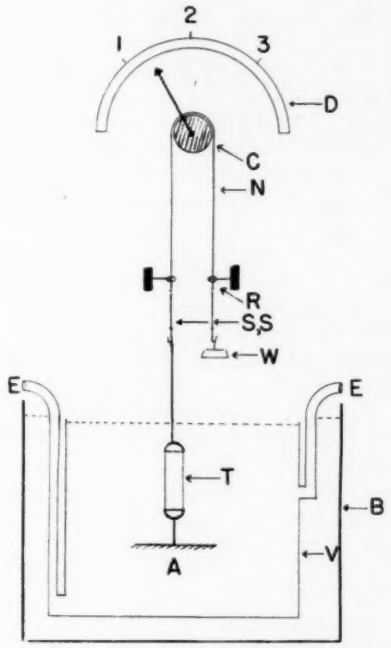

Fig. 1.—*A*, fixed anchorage of tissue strip; *B*, thermostatic bath; *C*, horizontal cylinder in jeweled bearings, carrying pointer; *D*, dial of arbitrary scale; *E*, *E*, entrance and exit tubes communicating with chamber; *N*, nylon fiber looped over rotable cylinder; *R*, steadying rings; *S*, *S*, silk fibers joined to ends of nylon fiber; *T*, tissue strip in its clamps; *V*, vessel serving as chamber, containing experimental solution; *W*, weight, comprising counterweight together with actual load on muscle.

springs against known weights; besides, the spring resistance increased in degree, as tensed and equal units of deflection of the recorder did not correspond to equal changes in strength of the muscle contraction. In the new design[4] (fig. 1) a horizontal cylinder minimal in weight and inertia, mounted in low-friction jeweled bearings, was substituted for the coiled springs. A single nylon fiber passes over

4. This instrument was used in the laboratory by permission of the Frederick Stearns Company.

the cylinder, and each end passes through a steadying ring, to terminate in a silk fiber carrying a minute hook. One hook engages the muscle while the other carries a weight to balance exactly the weight of the muscle and its holding clamps. Thus any additional weight represents the known actual load on the muscle, and a constant resistance is offered regardless of the extent of contraction. A delicate aluminum pointer fixed to the horizontal cylinder indicates over an arbitrary scale each unit of which corresponds to a vertical movement of 0.9 mm. on the part of the suspended hook. It is possible to compute the actual percentage of contraction of the muscle with such an indicator, but this would have little meaning since the initial degree of contraction of the smooth muscle, due to tonus, is unknown. Two different strips, equal in length, may differ considerably as to cross sectional area of actual contractile substance. The scale readings were consequently read directly and plotted manually. Other factors, such as p_H, temperature and solutions, have been successfully regulated as in previous work.[5] Albino rabbits were killed by a blow at the base of the skull, and the eyes were immediately enucleated. The radial strip of iris was cut out, mounted in clamps and weighed in aerated Sollmann-Rademaker solution [5a] at 33 C. ± 0.2 C., the same temperature at which the strip was kept during the experiment. The p_H was controlled at 7.5 ± 0.1 (LaMotte). The muscle was fixed to the apparatus in identical solution in a chamber containing 200 cc. and loaded, usually with a weight in the neighborhood of 20 mg. This was the actual resistance against which the contractive effort was expended. The excised section [6] was allowed to adjust itself to the load and to recuperate from all manipulations for fifteen minutes. After this initial period the pointer was set to mark 3 on the scale, thus giving all experiments a common starting point. During the first three minutes the position of the pointer was checked every minute and then every third minute until the drug was introduced by means of a syringe. The amount of drug was such as to bring the contents of the entire chamber to a predetermined concentration. From this moment the position of the pointer was checked every fifteen seconds until the muscle finished its first quick reaction and settled down to a new fairly constant length. Thereafter, readings were taken at half minute and minute intervals, depending on the rate of change exhibited by the muscle. The points thus recorded were plotted (fig. 2).

The experiments were organized in the following way: Contractions were produced either by epinephrine hydrochloride [7] or neo-synephrin hydrochloride (experiments 1, 2, 3, 4 and 5). Readings were taken until the muscle steadied to a fairly constant length, which took about

5. Donatelli, L., and Wiechmann, R.: Sulla farmacologia della musculatura liscia dell iride funzionante in vitro, Boll. Soc. ital. di biol. sper. **13**:101 (Feb.) 1938. Gunter, M., and Mulinos, M. G.: The Reaction of the Isolated Sphincter of the Pupil to Autonomimetic Drugs, Arch. internat. de pharmacodyn. et de therap. **62**:33 (May 31) 1939. Seager, L. D.: The Effect of Potassium Chloride on the Normal and Denervated Iris, J. Pharmacol. & Exper. Therap. **66**:202 (June) 1939. Heath and Geiter.[1]

5a. The composition of this solution on the basis of 100 cc. follows: sodium chloride, 0.9 Gm.; potassium chloride, 0.04 Gm.; calcium chloride, 0.024 Gm.; sodium bicarbonate, 0.03 Gm., and dextrose, 0.1 Gm.

6. There was no appreciable difference between material from a fresh eye and from one refrigerated for as long as forty-eight hours.

7. This preparation was free of choloretone and especially manufactured by Parke, Davis & Co.

twelve to fifteen minutes.[8] A solution of atropine sulfate was then added (experiments 2, 3, 4 and 5). This procedure was reversed in experiments 6, 7 and 8. Here, the first drug applied was atropine and the second epinephrine or neo-synephrin. The paired curves relate to the same iris strip, used a second time, after the drugs used in the preceding experiment had been washed out.

RESULTS

Experiment 1 (albino rabbit; dilator strip, fresh; load, 19.7 mg.).—During the first fifteen minutes a slight spontaneous contraction occurred. At fifteen minutes enough 1 per cent solution of neo-synephrin hydro-

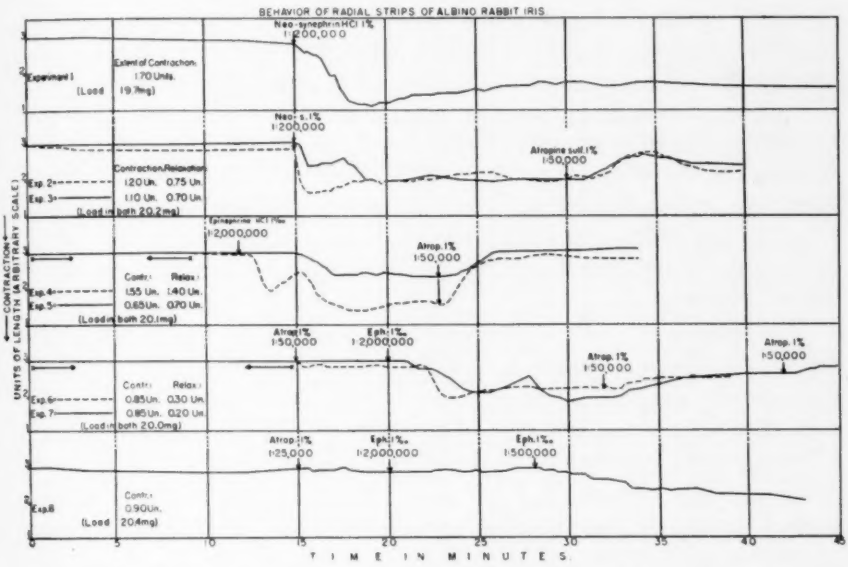

Fig. 2.—Chart showing the behavior of radial strips of iris of albino rats. In experiments 4 and 5 and 6 and 7, x⟶ ⟵x includes the portion of the tracing common to both experiments. In experiment 6 the slight contraction at fifteen minutes is an artefact. The concentrations of the drugs are expressed thus: for 1:100, 1%; for 1:1,000, 1‰.

chloride was applied to afford a concentration of 1:200,000. An immediate single contraction appeared. Its maximal extent was reached after four and a quarter minutes and corresponded to 1.70 scale units. After this maxium there was a slight relaxation, but, by and large, the strip remained contracted during the thirty minutes of observation after the application of the drug. Every muscle strip shows individual behavior,

8. Only a few curves are given (fig. 2) as typical of many.

so that only observations extended over a longer period can furnish a basis for judgment on its reaction to a drug. There were no sudden relaxations which might be interpreted as a reaction to a relaxing drug. Experiment 1 is typical of many similar tests.

Experiments 2 and 3 (albino rabbit; dilator strip, refrigerated forty-eight hours; load, 20.2 mg.).—At fifteen minutes a 1 per cent solution of neo-synephrin hydrochloride was applied, giving a concentration of 1 : 200,000. An immediate contraction appeared in both experiments, accomplished in a single step in experiment 2 but in two steps in the second trial with the same strip (after washing, experiment 3).[9] The maximal extents of contraction in experiments 2 and 3 were 1.20 and 1.10 scale units, respectively. Neither curve shows sudden relaxations. At thirty minutes a 1 per cent solution of atropine sulfate was applied, so that the concentration equaled 1 : 50,000. Definite relaxations appeared, of 0.75 (experiment 2) and 0.70 (experiment 3) scale units. No stress should be put on the exact duration of delay between the application of the drug and the reaction of the muscle, since the rate of diffusion of the drug cannot be exactly controlled. Both curves show, after this relaxation by atropine, an immediate second contraction, which is less distinct in experiment 3. The total amount of the initial contraction by neo-synephrin had not been neutralized by the relaxation due to atropine.

Experiments 4 and 5 (albino rabbit; dilator strip, fresh; load, 20.1 mg.).—At twelve minutes a 1 : 1,000 solution of epinephrine hydrochloride was applied, giving a concentration of 1 : 2,000,000. Experiment 4 shows the two step type of contraction with a maximal extent of 1.55 scale units. Neither curve shows any sudden or marked relaxation. At twenty-three minutes a 1 per cent solution of atropine sulfate was applied, so that the concentration equaled 1 : 50,000. There were definite relaxations, of 1.40 (experiment 4) and 0.70 (experiment 5) scale units.

The initial contraction in experiment 4 was not fully neutralized by atropine, which is the customary finding. The unusually weak contraction in experiment 5 was, it so happened, completely abolished by atropine.

In all, 6 experiments identical with experiments 4 and 5 have been carried out, in which the dilator contracted with epinephrine hydrochloride was relaxed by atropine sulfate, and 8 experiments identical with experiments 2 and 3, proving the same relaxation to occur in the dilator contracted with neo-synephrin hydrochloride. The results in all were the same as those shown in figure 2.

9. In identical pairs of experiments (not included in figure 2) it was as commonly found that the two step type of contraction occurred without any previous washing.

Experiments 6 and 7 (albino rabbit; dilator strip, fresh; load, 20 mg.).—At fifteen minutes a 1 per cent solution of atropine sulfate was applied to give a concentration of 1 : 50,000. Five minutes later enough 1 : 1,000 solution of epinephrine hydrochloride was added to make the concentration 1 : 2,000,000. The ensuing contraction of 0.85 scale units in both experiments (of extended two step form in experiment 7) demonstrates that this dose is strong enough to overcome any contraction-inhibiting tendency that atropine may have.

After the attainment of a new level in experiment 6 (at thirty-two minutes), a second application of atropine was made with the same absolute amount of solid drug as at the fifteen minute application. It was followed by a slight relaxation (0.30 scale units). Similarly, in experiment 7 a second dose of atropine after stabilization (at forty-two minutes) brought about a slight relaxation (0.20 scale units). This is proof that the strip had not been damaged by the original dose of atropine and that the response to epinephrine being partially overcome by still more atropine, the total dose of the latter was within physiologic limits.

If neo-synephrin hydrochloride is applied instead of epinephrine hydrochloride, a concentration of 1 : 200,000 overcomes a concentration of 1 : 50,000 previously applied atropine sulfate (curves not published).

Experiment 8 (albino rabbit; dilator strip, refrigerated twenty-four hours; load, 20.4 mg.).—At fifteen minutes a 1 per cent solution of atropine sulfate was applied, affording a concentration of 1 : 25,000—twice as high as in any of the other experiments. Five minutes later a 1 : 1,000 solution of epinephrine hydrochloride was applied to give a concentration of 1 : 2,000,000. There was no contraction, indicating that the dose of atropine had been high enough to inhibit completely the response to epinephrine. This inhibition was not due to the transcension of physiologic limits, since a second dose [10] of epinephrine eight minutes later resulted in a distinct, extended contraction.

COMMENT

These experiments on isolated dilator muscles raise several questions:

1. Is the antagonism between epinephrine (or neo-synephrin) and atropine restricted to the isolated muscle or does it play a role also in the intact eye? The latter would be contrary to the widespread assumption of a synergistic action of these drugs. Recent clinical observations seem to point in the direction of a definite antagonistic action on the human iris muscle.

10. This concentration equaled 1 : 500,000 in addition to the concentration of 1 : 2,000,000 already present.

2. What is the mechanism of the atropine effect? It certainly is not the result of a toxic action damaging to the muscle and interfering with its contractility. This is proved by experiments 2 and 3, which show a new contraction after atropinization, and by experiments 6, 7 and 8, which demonstrate a contraction by epinephrine after atropinization. The experiments do not offer definite clues as to the locus of action, whether it is in the contractile substance or more peripheral. Further experiments are in progress to attempt the elucidation of this matter. Preliminary experiments concerning the action of strychnine salts cast a doubt on the assumption that the antagonism between sympathic and parasympathic drugs is specifically limited, for strychnine, which belongs to neither class, can be substituted for atropine and has been found to exercise a relaxing effect on a preparation treated with epinephrine neo-synephrin.

The results of these experiments with the isolated dilator strip do not justify the assumption that an organ belonging to the sphere of the autonomic nervous system must necessarily be equipped with two nerve supplies, if it reacts to both groups of autonomomimetic drugs. Reaction to such drugs does not seem to us (especially in the light of the effects of strychnine) to be a sufficient basis for the assumption of a "corresponding" innervation. The reaction of the same tissue to members of both classes of drugs is insufficient reason for belief in a double innervation.

CONCLUSION

Isolated radial strips of the iris dilator of albino rabbits are contracted by epinephrine and neo-synephrin in physiologic doses. Application of atropine relaxes the contracted dilator. The amount of the effect is dependent on the relative concentrations of the antagonistic drugs.

SYMPATHETIC OPHTHALMIA

A CLINICAL REVIEW OF SIXTY-THREE CASES

RODMAN IRVINE, M.D.
LOS ANGELES

This report is based on a study of the histories of cases of sympathetic uveitis recorded at the Massachusetts Eye and Ear Infirmary between 1922 and 1935. A previous report evaluating the results of treatment of this disease with injections of diphtheria antitoxin in large doses, as proposed by Verhoeff,[1] was read at the 1935 meeting of the New York State Medical Society.[2] Beneficial results from this treatment were seen in 75 per cent of the patients so treated.

The clinical findings in 37 cases in which the diagnosis was proved by pathologic examination and in 26 cases in which it was not proved but in which the clinical course was typical of this specific uveitis are included here. Analysis of any series of records of such an infrequent condition emphasizes many of its features not generally appreciated and focuses attention on controversial ideas regarding its nature, thus pointing out what further observations should be made for a better understanding of the disease. The data for this entire series are summarized in table 1. In analyzing clinical material, general trends rather than individual instances are important, since case histories are not always accurate and are seldom complete.

INCIDENCE

Eighty-four per cent of the patients were males and 16 per cent females. Twenty-four per cent were under 12 years of age, 34 per cent were between 12 and 50 and 42 per cent were over 50 years. Since the absolute frequency of injuries and operations in these age groups is not known, the percentages do not signify that sex or age influence the incidence. The patients in one proved and 1 unproved case were Negroes. Green [3] also reported an instance of sympathetic ophthalmia occurring in a Negro.

Wright,[4] from Southern India, and Mulock Houwer,[5] from Java, raised the question of race and climate affecting the disease, stating that

1. Verhoeff, F. H.: Arch. Ophth. **61**:28, 1927.
2. Verhoeff, F. H., and Irvine, S. R.: New York State J. Med. **36**:1, 1936.
3. Green, J.: Am. J. Ophth. **5**:295, 1922.
4. Wright, R. E.: Proc. All-India Ophth. Soc. **4**:1, 1935.
5. Mulock Houwer, A. W.: Peculiarities of Well-Known Ocular Diseases in the Netherland East Indies, Arch. Ophth. **21**:235 (Feb.) 1939.

TABLE 1.—*Summary of Clinical Findings*

Case; Age, Yr.; Sex	Month of Onset	Nature of Injury	Time From Injury to Onset of Sympathetic Involvement, Weeks	Time From Injury to Enucleation, Weeks	Time From Onset of Sympathetic Involvement to Enucleation, Days	Degree of Irritability of Exciting Eye; at Onset of Symptoms in Sympathizing Eye		Keratic Precipitates	Early Stage: Synechiae (Involvement of Anterior Segment)
Proved Cases									
1 50, F	June	Perforation of hypopyon ulcer; lens in wound	15	16	12	+	E. S.	0 +	Atrophic iris +
2 41, F	April	Cataract extraction; prolapse of iris....	10	11	7	+	E. S.	.. ++	Phthisis bulbi +
3 8, F	June	Perforation of cornea; prolapse of iris..	4	13	63	+ but less than sympathizing eye	E. S.	.. ++	Phthisis bulbi +
4 53, M	Nov.	Cataract extraction; lens substance in wound (?)	8	9	7	+	E. S.	.. 0	Cornea cloudy ++
5 70, M	Jan.	Cataract extraction; incarceration of lens capsule and iris	8	16	30	?	E. S.	.. +++	From injury 0
6 26, M	Dec.	Laceration of cornea; incarceration of iris; cataractous lens	2½	8	35	+ but less than sympathizing eye	E. S.	.. ++	From injury 0
7 43, M	Oct.	Intraocular foreign body; perforation of cornea and iris; cataract	8	9	7	++	E. S.	.. ++	++ ..
8 6, M	Nov.	Perforation of cornea; incarceration of iris	7	7	1 (?)	?	E. S.	.. +	From injury 0
9 66, M	June	Hemorrhagic glaucoma; trephine operation (infected wound); later iridotasis	5	4	—7	Enucleation	E. S.	.. +++	Enucleation ..
10 40, M	June	Intraocular foreign body; perforation of cornea; incarceration of iris; cataract	7	10	21	+	E. S.	.. ..	From injury 0
11 30, F	May	Perforation of limbus; cataract; 24 yr. later rupture of globe	8	6	—14	Enucleation	E. S.	.. +	Enucleation ..
12 60, M	Aug.	Perforation of limbus; incarceration of iris; cataract	12	12	2	+	E. S.	.. ++	Obscure ..
13 68, M	Feb.	Cataract extraction (extracapsular); incarceration of iris and lens capsule (?)	16	..	..	?	E. S.	.. ++	From injury +
14 9, M	?	Perforating wound with nail.....	4½	4½	1	?	E. S.	.. ++	No details ..
15 10, M	July	Perforation of cornea; prolapse of iris and lens	3	3	1	+	E. S.	.. ..	Obscure ++
16 5, M	Jan.	Perforation of cornea; prolapse of iris; cataract	9	238	1,550	++	E. S.	.. ++	+++ +
17 6, M	Sept.	Perforating wound; prolapse of iris.....	6	6	1	+	E. S.	.. ++	Phthisis bulbi +
18 69, M	Sept.	Glaucoma; iridectomy; incarceration of iris; lens injured	—10	14	30	+	E. S.	++ +	++ 0
19 37, M	June (Negro)	Rupture of limbus; incarceration of iris; lens dislocated	6	6	40	+	E. S.	.. ++	Obscure +
20 11, M	?	Perforation of limbus; incarceration of iris and lens	6	2	—28	++	E. S.	.. ++	Enucleation 0
21 10, M	?	Perforation of cornea; cysts of iris.....	16 (?)	..	..	+	E. S	+ +	From injury ..
22 45, M	April	Hemorrhagic glaucoma; operation for glaucoma; incarceration of lens capsule in wound	32	34	14	++	E. S.	.. ++	From injury ..
23 54, M	May	Orbital abscess; perforation of cornea; phthisis bulbi	10	12	14	+	E. S.	.. ++	Phthisis bulbi +
24 38, M	April	Perforating wound in ciliary body; prolapse of iris; rupture of lens	8	8	1	++	E. S.	.. ++	Obscure Iris normal

* In this table E indicates the exciting eye; S, the sympathizing eye; +, mild; ++, moderate; +++, marked; +++, marked; K. P., keratic precipitates, and L. P., light perception. The minus signs before numerals indicate a negative time tion; that is, enucleation was done before symptoms of sympathetic disease developed. Leaders mean that there was no mention on the record of the condition indicated.

† In the "proved" cases the diagnosis was confirmed by microscopic examination of the enucleated eye or a piece of it either Dr. Verhoeff or Dr. Terry.

Clinical Course								
	Maximum Reaction							
Vision	Keratic Precipitates	Synechiae (Involvement of Anterior Segment)	Opacities of Vitreous	No. of Exacerbations	Years Case Was Followed	Years Not Active	Final Vision	Pathologic Report †
L. P. 20/40	.. ++	Enucleation ++	.. ..	2	8	7½	S.: 20/30	Marked sympathogenic infiltration of iris; slight infiltration of ciliary body and choroid
L. P. 7/200 (cataract)	.. +++	Enucleation +++	.. ..	2	2½	1½	S.: 20/30	Early mild sypathetic involvement
20/200 20/30	+ ++	Enucleation +	.. ++	2	4⅓	4	S.: 20/40	Early sympathetic infiltration of ciliary body, iris and choroid near ora serrata
Nil 20/50	.. ++++	Enucleation +	.. ..	2	8 5/12	8	S.: 20/100 (cataract)	Moderate sympathetic involvement, confined to choroid
L. P. 1/200 (cataract)	.. +	Enucleation +	.. ..	0	1⅓	1	S.: 20/30	Recent mild sympathetic involvement, primarily of ciliary body and iris
L. P. 20/50	.. ++	Enucleation +	.. Clear	1	4⅙	3⅚	S.: 20/15	Marked sympathetic involvement of entire uveal tract
L. P. 20/15	.. ++	Enucleation 0	.. ++	0	2 7/12	2	S.: 20/15	Marked sympathogenic involvement of entire uveal tract; inflammatory cells in lens
L. P. 20/20	.. ++	Enucleation +	.. +	1	9½	9	S.: 20/20	Recent sympathogenic uveitis
..... 20/25	.. +++	Enucleation +	.. ++	1	1⅚	0	S.: 20/70 (cataract)	Mild sympathogenic infiltration of choroid and iris
L. P. 20/30	++ +++	++ 0	Obscure ..	2	2⅚	2	S.: 20/20	Marked sympathogenic involvement of entire uveal tract
..... 20/20	.. +++	Enucleation ++	.. ..	0	9⅓	8⅚	S.: 20/20	Early sympathogenic involvement of exciting eye; early sympathogenic involvement of iris of sympathizing eye
..... 20/30	.. ++	Enucleation ..	.. +	1	2¾	0	S.: 20/50 (cataract)	Marked sympathogenic involvement of ciliary body and choroid
20/200 (cataract)	+ +++	.. ++	+ ..	0	2	1½	E.: 20/50 S.: 20/200	Iris specimen from exciting eye showed sympathetic infiltration
....	.. ++	Enucleation ..	.. ..	0	3¼	2 11/12	S.: 20/20	Typical early sympathogenic uveitis
..... 20/30	.. ..	Enucleation ++	.. Operation for glaucoma	2	13⅓	Glaucoma	S.: 20/70	Early sympathogenic uveitis
L. P. 20/20	++ ++++	+++ +++	± ++	8 (yearly for 8 yr.)	8½	0	S.: 20/20	Small widely scattered foci in choroid; appearance as in early stage of sympathetic involvement
..... 20/50	.. +++	Enucleation +	.. ++	3, 9 yr. between	13	0	S.: 20/30	Early sympathetic involvement; marked phacoanaphylactic endophthalmitis
Nil 20/20	.. +	Enucleation 0	.. +	0	8½	6 5/12	S.: 20/20	Sympathogenic infiltration; nests of epitheloid cells in choroid
L. P. 20/30	.. +++	Enucleation +	.. +	1	1¼	⅚	S.: 20/20	Marked sympathogenic uveitis
..... 20/100	.. ++	Enucleation 0	.. ++	0	1	0	S.: 20/20	Early sympathetic involvement, primarily of ciliary body and iris
2/200 20/20	++ +	++ ..	.. ..	3	?	0	S.: 20/20	Iris specimen: typical foci of sympathetic ophthalmia
Nil 20/70	.. ++	Enucleation ..	.. ++	0	13	12¾	S.: 20/40	Marked sympathetic uveitis, especially of choroid
..... 20/70	.. ++	Enucleation +	.. ++	0	½	0	S.: 20/50	Marked recent sympathetic ophthalmia
L. P. 20/30	.. +++	Enucleation ++	.. ..	2 (?) (Glaucoma)	6	5	S.: 4/200	Marked sympathogenic infiltration

TABLE 1.—*Summary of Clinical Findings in Su[illegible]ree Case[illegible]*

Case; Age, Yr.; Sex	Month of Onset	Nature of Injury	Time From Injury to Onset of Sympathetic Involvement, Weeks	Time From Injury to Enucleation, Weeks	Time From Onset of Sympathetic Involvement to Enucleation, Days	Degree of Irritability of Exciting Eye; at Onset of Symptoms in Sympathizing Eye		Keratic Precipitates	Early Stage: Synechiae (Involvement of Anterior Segment)	Clinical C[illegible] Vision
Proved Cases—Continued										
25 44, F	April	Hemorrhagic glaucoma; iridotasis; incarceration of iris	8	10	14	++	E. S.	++ +	+ ..	L. P. 20/40
26 19, M	June	Perforation of limbus; prolapse of iris; lens preserved; purulent (?)	8	8	1	+	E. S.	.. ..	Disorganized globe ++	..... "No 4/200
27 6, M	Dec.	Perforation of cornea and lens; incarceration of iris and lens	20	36	98	+	E. S.	0 +++	From injury +	L. P. L. P.
28 61, M	Dec.	Hemorrhagic glaucoma; iridectomy; incarceration of iris	7	8	5	+	E. S.	.. 0	From operation ++	Nil 20/50
29 11, M	Jan.	Perforating wound with BB shot; cataract	40	42	14	++	E. S.	.. ..	No details ++	..... ?
30 20, M	June	Perforation of limbus; incarceration of iris; cataract	8	..	..	++	E. S.	0 ++	++ 0	6/300 20/30
31 40, F	April	Glaucoma in each eye; iridectomy and iridotasis in right eye; previous operation for glaucoma in left eye	5	..	..	+	O.D. O.S.	.. ..	+++ +++	1/250 L. P.
32 8, M	June	Intraocular foreign body; incarceration of iris; cataract	4	3	−7	Enucleation	E. S.	.. ++	Phthisis bulbi +	L. P. 20/20
33 52, F	?	Glaucoma in each eye; iridectomy.....	?	?	..	?	E. S.	.. ..	No details No details	20/30 20/20
34 65, M	?	Intraocular foreign body; glaucoma; iridotasis in each eye	?	?	?	?	O.D. O.S.	.. ..	No details No details	20/100 4/200
35 58, F	Aug.	Glaucoma; iridotasis	3	6	21	++	E. S.	.. ++	Acute glaucoma ..	....
36 60, M	June	Cataract extraction; prolapse of iris and vitreous	8	104	665	++	E. S.	0 0	From operation +	20/30 20/200 (cataract)
37 ?, M	?	Intraocular foreign body; glass removed; traumatic cataract	?	?	?	?	E. S.	.. ..	No details No details	....
Unproved Cases										
38 55, M	Feb.	Iridotasis in each eye.....	5	..	..	+	O.D. O.S.	++ 0	0 ++	20/50 L. P.
39 5, M	Jan.	Perforation of cornea.....	12	..	..	+	E. S.	.. ++	++ ++	..... ?
40 57, M	May	Perforating wound	?	104	?	?	E. S.	.. ++	.. 0	..... 20/40
41 54, M	Jan.	Glaucoma; iridectomy	6	..	..	+	O.D. O.S.	++ ++	++ +	L. P. L. P.
42 8, M	Sept.	Perforating wound	28	..	..	+	E. S.	.. +	Hemorrhagic pigmented cornea ++	L. P. 20/70
43 50, M	Nov.	Perforation of cornea; prolapse of iris; Cataract	12	..	..	++	E. S.	+ ++	From injury 0	L. P. 20/20
44 63, M	May	Perforating wound; hypopyon.....	10	7	−21	Enucleation	E. S.	.. ++	Enucleation +	..... 20/70
45 66, M	Dec.	Cataract extraction	12	..	..	+	E. S.	.. ++	++ +++	L. P. .....
46 54, ?	Feb.	Glaucoma; trephining of left eye; iridectomy on right eye ten days previously	3	..	..	+	O.D. O.S.	++ 0	+ ++	20/20 7/200
47 45, F	Aug.	Glaucoma; iridectomy	4	..	..	+	E. S.	+ ++	Before operation +	L. P. 20/20
48 71, M	Aug.	Cataract extraction; incarceration of iris in each eye within ten days	3	..	..	+	O.D. O.S.	++ +	.. ..	20/300 20/30
49 38, M	Jan.	Perforation; intraocular foreign body...	4	3	−7	Enucleation	E. S	.. 0	Enucleation ++	....
50 40, M	April	Perforating wound; incarceration of iris; cataract	4	..	..	+	E. S.	0 +	From injury ..	L. P. 20/40
51 71, M	May	Cataract extraction; prolapse of iris....	12	24	110	+	E. S.	0 0	From operation ++	L. P. L. P.
52 50, ?	Jan.	Cataract extraction	2	..	..	+	E. S.	.. ..	No details No details	20/50 20/50

ree Cases of Sympathetic Uveitis—Continued*

Clinical Course								
Maximum Reaction								
Vision	Keratic Precipitates	Synechiae (Involvement of Anterior Segment)	Opacities of Vitreous	No. of Exacerbations	Years Case Was Followed	Years Not Active	Final Vision	Pathologic Report †
L. P. 20/40	.. ++	Enucleation ++++	.. ..	4	4	1	S.: L. P.	Marked sympathogenic involvement of entire uveal tract
..... 4/200	"No K.P."(?) ..	Enucleation ++++	.. ..	..	1½ (Glaucoma)	½	S.: L. P.	Advanced sympathetic involvement especially of ciliary body and choroid
L. P. L. P.	.. ..	No details +++	.. ..	3	1¾	0	S.: L. P.	Marked sympathetic involvement chiefly of iris and ciliary body
Nil 20/50	.. ..	Enucleation ++	.. ..	2 Operation	1	½	S.: L. P.	Marked sympathogenic inflammation
..... ?	.. ..	Enucleation +++	.. ..	2	3 5/12	2½	S.: L. P.	Early sympathetic involvement of choroid
6/200 20/20	.. ++++	+++ +++	.. ..	4	3½	2	E.: Nil S.: L. P.	Advanced sympathogenic involvement; specimen of iris of exciting eye
2/200 L. P.	+ ++	+++ +++	.. ..	3	3⅙	0	O. D.: L. P. O. S.: Nil	Iris specimen; sympathetic infiltration
L. P. 20/20	.. +++	.. +++	.. ---	6	13⅚	13	S.: L. P.	Early sympathetic uveitis
20/30 20/20	.. ..	.. +++	.. ..	..	11	Glaucoma	E. Glaucoma S. Glaucoma	Recent sympathetic uveitis
20/100 4/200	.. ..	No details; glaucoma in each eye	..	? (Glaucoma)	6	0	O. D.: L. P.	Advanced sympathetic uveitis
....	.. ++	Enucleation No details	.. 0	0	⅙	0	S.: 20/200	Marked sympathetic uveitis
20/30 20/200 (cataract)	+++ +++	+++ Glaucoma	+++ Enucleation	4	2½	0	E.: 2/200	Sympathogenic uveitis
....	.. ..	Enucleation No details	.. ..	?	?	?	S.: L. P.	Typical sympathetic infiltration of choroid
20/50 L. P.	++ +	- ++	-- --	0	¼	0	O. D.: L. P. O. S.: 20/20	
..... ?	.. ++	+++ ++	.. ..	2	1	0	E.: Nil S.: Nil	
..... 20/40	.. ++	Enucleation 0	.. -	0	5	1	S.: 20/20	
L. P. L. P.	+++ ++	+++ ++	.. ..	1	1¾	0	O. D.: L. P. O. S.: L. P.	
L. P. 20/70	.. ++	.. +++	.. ..	?	7/12	0	E.: 20/70 S.: L.P.	
L. P. 20/20	.. ++	.. 0	.. ..	1	2	1⅓	E.: L. P. S.: 20/50	
..... 20/70	.. +++	.. ++	.. ++	2	12⅔	0	S.: L. P.	
L. P.	.. ++	++ +++	.. ..	1	¼	0	E.: L. P. S.: 4/200	
20/20 7/200	++ +	+ ++	++ ++	1	1	¼	O. D.: 20/15	
L. P. 20/20	++ ++	+++ +	+++ ++	1	1	⅔	E.: L. P. S.: 20/20	
20/200 20/20	++ +	.. ..	.. +	0	¼	0	O. D.: L. P. O. S.: L. P.	
....	.. 0	.. ++	.. ..	0	1	⅚	S.: 20/20	
L. P. 20/40	"No K.P." ++	.. +	.. --	3	3	0	E.: L. P. S.: Nil	
L. P. L. P.	0 ..	.. +++	.. ..	1	1¼	0	S.: Nil	
20/50 20/50		No details No details		1	2½	2	E.: 20/20	

TABLE 1.—*Summary of Clinical Findings in Three Cases*

Case; Age, Yr.; Sex	Month of Onset	Nature of Injury	Time From Injury to Onset of Sympathetic Involvement, Weeks	Time From Injury to Enucleation, Weeks	Time From Onset of Sympathetic Involvement to Enucleation, Days	Degree of Irritability of Exciting Eye; at Onset of Symptoms in Sympathizing Eye		Keratic Precipitates	Early Stage: Synechiae (Involvement of Anterior Segment)	Vision
Unproved Cases—Continued										
53 54, F	?	Perforating wound; cataract	?	?	?	?	E. S.	.. ++	Phthisis bulbi ++	..... 20/200
54 21, M	?	Perforating wound	8	?	?	?	E. S.	.. +	.. ++	..... L. P.
55 54, M	April	Rupture of sclera; prolapse of ciliary body	3	..	..	+	E. S.	+ +	From injury +	10/200 20/200
56 25, M	Dec.	Perforation of ciliary body; panophthalmitis; evisceration	164	8	—3 yr.	Evisceration	E. S.	.. ++	Evisceration 0	..... 20/20
57 29, M	Dec.	Perforation of cornea	12	260	250	+	E. S	0 +++	++ ++	L. P. 20/100
58 40, F	Dec. (Negro)	Perforation of limbus; prolapse of ciliary body	4	..	..	+	E. S.	+++ +++	From operation 0	20/70 20/50
59 7, M	Dec.	Perforation of cornea; purulent endophthalmitis	30 (?)	32	1	?	E. S.	.. ++	Obscure +	..... 20/20
60 52, M	July	Intraocular foreign body; perforation of cornea and lens	8	..	..	?	E. S.	.. ..	Obscure ++	..... 20/100
61 53, M	July	Cataract extraction	3	..	..	+	E. S.	.. ++	++ +	L. P. 20/20
62 6, M	?	Perforating wound	<30	2	—?	Enucleation	E. S.	.. ..	Enucleation Corneal scars ++	..... L. P.
63 25, M	?	Operation for strabismus (infection); perforation	?	468	?	+	E. S.	.. ++	No details +	..... L. P.

it had but rarely occurred in their experience and that the disease in the few cases they had seen was unusually mild. Contrary to these impressions, Mohamed [6] recently reported 27 cases of sympathetic ophthalmia collected at the Giza Institute of Ophthalmology in Cairo in fifteen years, indicating then that the condition is not rare in Egypt, and Narayano [7] reported 13 cases following 479 traumatic injuries (2.7 per cent) in southern India within four years.

Waldmann,[8] finding a seasonal incidence of 75 per cent in the winter months, attempted to correlate the condition with infections of the upper respiratory tract. Trowbridge's [9] analysis of 35 cases showed no such correlation with seasons. About an equal number of the cases reported here occurred in the winter months (November through April) as in the summer months. Here again the relative incidence of injuries in these seasons, necessary for establishing a causal relationship, is unknown.

6. Mohamed, I. A.: Bull. Ophth. Soc. Egypt **29**:168, 1936.
7. Narayano: Proc. All-India Ophth. Soc. **5**:223, 1936.
8. Waldmann, B.: Am. J. Ophth. **20**:625, 1937.
9. Trowbridge, D. H.: Am. J. Ophth. **20**:135, 1937.

*Three Cases of Sympathetic Uveitis *—Continued*

Clinical Course								
	Maximum Reaction							
Vision	Keratic Precipitates	Synechiae (Involvement of Anterior Segment)	Opacities of Vitreous	No. of Exacerbations	Years Case Was Followed	Years Not Active	Final Vision	Pathologic Report †
.....	..	Enucleation	..	?	20	0	S.: L. P. (glaucoma)	
20/200	++	+++	..					
.....	..	Enucleation	..	?	7	4	S.: L. P.	
L. P.	+	++	..					
10/200	..	..	..	0	1⅙	0	E.: 12/200	
20/200	+	+	++				S.: 20/100	
.....	..	..	..	0	15	12	S.: 20/15	
20/20	++	0	++					
L. P.	..	+++	..	4	14	0	E.: Enucleation	
20/100	+++	++	+++				S.: L. P.	
20/70	+++	++	++	1	1⅙	0	E.: 20/20	
20/50	+++	+	++				S.: 20/30	
.....	..	Enucleation	..	0	6	5	S.: Nil	
20/20	++	+++	+++					
.....	..	..	..	3	20½	3	E.: L. P.	
20/160	+++	+++	..				S.: L. P.	
L. P.	..	++	+++	0	¾	0	E.: L. P.	
20/20	++	+	+				S.: 20/20	
.....	..	Corneal scars	..	0	11	4⅛	S.: 20/20	
L. P.		++++						
.....	..	Enucleation	..	?	22	10	S.: 20/70	
L. P.	++	+	++					

FREQUENCY

To estimate the frequency with which sympathetic ophthalmia followed perforating injuries at the Massachusetts Eye and Ear Infirmary, only cases in which sympathetic ophthalmia occurred while the patients were under observation were usable. Of 1,976 cases of injury, there were 25, or approximately 1.26 per cent, in which sympathetic ophthalmia developed. Thirty-one additional cases of sympathetic ophthalmia following injury were seen during this period, but as the patients had sympathetic ophthalmia when first seen the cases were not usable for the estimation of frequency.

Table 2 gives the frequency of occurrence of sympathetic uveitis following injuries as reported by various authors. The more recent reports show a 1 or 2 per cent incidence, with the exception of those of Wright and Houwer, whereas the early reports show a much higher frequency. This high frequency probably resulted because these early observers were dealing with severe injuries improperly treated as regards sepsis, closure of the wounds and promptness of enucleation of hopelessly damaged eyes. The method of treatment to insure proper closure of the wound, as discussed later, may have an important bearing

on the frequency. The impression held by many ophthalmologists that sympathetic ophthalmia complicates injuries so rarely that the plan of treatment of the injured eye need not be influenced by the possibility of this complication is not confirmed by the average 1 per cent frequency of incidence following traumatic perforation of the globe. Realization of this frequency should lessen tampering with an eye useless from any cause when the opposite eye has useful vision. The possibility of the condition going undiagnosed by persons in industrial practice is readily

TABLE 2.—*Frequency of Occurrence of Sympathetic Ophthalmia*

Author	Year	Nature of Injury	No. of Cases Analyzed	Sympathetic Ophthalmia, %
Weekers, L.: Ann. d'ocul. **154**: 196, 1917	1870	War injuries	...	55
Weekers: Ibid.	1870	Peace injuries	...	12
Würdemann, H. V.: Injuries of the Eye, Chicago, Cleveland Press, 1912	American War of Rebellion		274	16
Fuchs, E.: Arch. f. Ophth. **61**: 365, 1905	1905	Injuries	200	13
Guy, W. A.: Brit. J. Ophth. **17**: 15, 1933	1933	Injuries of posterior segment	53	10
Wright [4]	1935	Wounds in India	15 seen in 15 yr.	
Mohamed [6]	1936	Injuries seen at Giza Institute, Cairo	27 seen in 15 yr.	
Mulock Houwer [5]	1939	Wounds in Java	...	Rare
Narayano [7]	1936	Traumatic injuries	479	2.7
Theobald, G.: Am. J. Ophth. **13**: 597, 1930	1930	Operations and injuries	11,831	0.45
Duggan, W. F.: Arch. Ophth. **10**: 768 (Dec.) 1933	1933	Intraocular foreign bodies	270	0.74
Bennetto, F. R.: Canad. M. A. J. **23**: 668, 1930	1930	Perforating wounds	200	1
Dollfus, M. A., and Halbron, P.: Arch. d'opht. **51**: 365, 1934	1934	Injuries	394	1.27
de Schweinitz, G. E.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1924	1924	Severe injuries	...	2 to 3.5
Massachusetts Eye and Ear Infirmary	1922-1935	Perforating injuries	1,976	1.26

understood when one considers how many times important clinical signs have gone unrecognized until "sensitization" to them has developed. On the other hand, ophthalmic surgeons having a large industrial practice might see sympathetic ophthalmia with less than average frequency, because their method of closing and treating wounds of the eye is more skilful than that used in clinics, from which the foregoing statistics were gathered.

Data on the frequency with which operative wounds were complicated by sympathetic ophthalmia were not available from the records reviewed, as many of the operations were done elsewhere, and in many instances multiple operations had been performed on the eyes in a single case. However, the percentage of total cases of sympathetic ophthalmia

in this series in which operative wounds were the exciting cause is surprisingly high. The condition in 37 per cent of 37 proved cases and in 31 per cent of 26 unproved cases followed operative procedures.

ETIOLOGY

No record was found at the Massachusetts Eye and Ear Infirmary of sympathetic ophthalmia occurring without there having been operative or traumatic perforation of the globe prior to its onset. One eye not included in this series contained a melanotic sarcoma of the choroid, and the adjacent uvea showed perivascular infiltration resembling that seen in sympathetic uveitis. This eye had been operated on previously for glaucoma, and there was no clinical evidence of sympathetic uveitis in the other eye. Two other eyes showing sarcoma and infiltration suggesting sympathetic uveitis were seen in the laboratory, but in both of these there had been previous operations, and data regarding the condition of the fellow eye were not available. There are reports in the literature [10] describing sympathetic uveitis in sarcomatous eyes without perforation. The rarity of these indicates that further confirmation of the absence of perforation or operative intervention is needed. In 2 of the cases of sympathetic ophthalmia accompanying sarcoma cited by Morax,[11] there was posterior scleral rupture.

The exceptional instances of the disease occurring from trauma without perforation, cited in the literature, are so rare as to make one wonder not so much that they occurred without perforation but that a perforation may have been overlooked. The condition has been reported as resulting from rupture of the posterior segment without any contamination of the wound by the conjunctival sac.[11] Andersson [12] reported a case considered to be one without perforation until serial sections showed a small needle-sized puncture 10 mm. behind the limbus. Lamb,[13] reviewing cases in which the disease was said to follow injuries without perforation, discredited all except 1 in which no perforation was found, but in this case serial sections of the globe were not made, a requirement apparently necessary in view of Andersson's case.

In 2 of the proved cases (1 and 23) the sympathetic ophthalmia followed spontaneous perforation from pyogenic infection. Among the

10. (*a*) Morax, V.: Arch. d'opht. **1**:361, 1933. (*b*) Schwartz, F.: Am. J. Ophth. **10**:35, 1927. (*c*) Meller, J.: Arch. f. Ophth. **62**:167, 1905. (*d*) Reis, W.: ibid. **80**:69, 1912. (*e*) Lamb, H.: Tr. Am. Ophth. Soc. **29**:288, 1931. (*f*) Mass, M. M., and Shepkalova, V. M.: Vestnik oftal. **16**:390, 1938. (*g*) Fuchs, E.: Arch. f. Ophth. **61**:365, 1905.

11. Morax, V.: Ann. d'ocul. **169**:637, 1932.

12. Andersson, E.: Acta ophth. **16**:119, 1938.

13. Lamb, H. D.: Sympathetic Ophthalmia from Nonperforating Trauma: Report of Case, Arch. Ophth. **7**:97 (Jan.) 1932.

unproved cases there were 2 instances of sympathetic reaction in spite of pyogenic infection in the exciting eye (cases 56 and 63). The microscopic examination in 2 other cases (cases 7 and 17) revealed a phacoanaphylactic reaction characterized by the presence of pus cells in the lens. De Veer[14] reported the same finding in 1 case. Shahan,[15] Samuels[16] and others have noted the development of sympathetic ophthalmia in eyes with pyogenic infection. Probably the reason for the opinion that pus per se precludes sympathetic ophthalmia is that purulent eyes are removed or destroyed before the disease has had time to occur.

For consideration of the type of perforating injury most likely to result in this specific complication, the present series of cases was divided into those in which sympathetic ophthalmia followed accidental trauma and those in which it followed operations. In 66 per cent of the proved cases the disease followed injury. In every instance injury was severe, traumatizing uveal pigment and usually the lens. In the reports of cases 8, 14, 21 and 23 the condition of the lens was not mentioned, and in that of case 26 the lens was described as not involved. In all proved cases there was incarceration of uveal tissue or lens substance in the wound except 3 (cases 14, 21 and 23), in which the condition of the wound was not described. There was special mention of injury to the ciliary body in only 5 of these cases.

In the proved and unproved cases in which sympathetic ophthalmia followed operation, it followed cataract extraction in 11, iridotasis in 5, iridectomy in 5 and trephining in 1. In all 13 of the proved cases in the postoperative series there was incarceration of substance in the wound. In the 5 cases in which cataract extraction was done there were lens material and uveal tissue in the wound, and in the 8 cases in which operation was done for relief of glaucoma there was incarceration of uveal tissue in the wound. Four of the glaucomatous eyes (cases 9, 22, 25 and 28) showed hemorrhagic glaucoma. Had this diagnosis been recognized, the operation to relieve the glaucoma would not have been justified, as the unaffected eye in these 4 cases had vision of 20/50 or better. Fuchs[17] reported 100 cases of sympathetic ophthalmia in 8 per cent of which the ophthalmia developed after operation for absolute glaucoma, again emphasizing the risk of operating on useless eyes.

Common features of the wounds producing sympathetic ophthalmia were the severity of the trauma and the presence of prolapsed intraocular tissue. Since the majority of perforating injuries result in some

14. de Veer, J. A.: Arch. Path. **17**:663 (May) 1934.

15. Shahan, W. E.: Am. J. Ophth. **10**:120, 1927.

16. Samuels, B.: Panophthalmitis and Sympathetic Ophthalmia, Arch. Ophth **20**:804 (Nov.) 1938.

17. Fuchs, A.: Arch. de oftal. de Buenos Aires **7**:67, 1932.

incarceration of uveal or lens material and yet sympathetic uveitis develops after relatively few injuries, this factor of incarcerated substance in the wound would lose etiologic significance were it not for the findings in the cases in which the condition occurred after operation. All eyes were seen by pathologic examination to have had incarceration of lens or uveal tissue in the wound and to have been severely traumatized. One wonders then as to the likelihood of sympathetic ophthalmia occurring after operations with well approximated wounds healing by first intention. Samuels,[18] from his pathologic study of eyes exciting the specific infiltration, stated that the wounds showed evidence of poor healing. The foregoing considerations have influenced Verhoeff [19] to abandon iris inclusion operations for glaucoma.

In repairing injuries, to guard against inclusion of substance in the wound and to insure rapid healing I propose closing the scleral or corneal edges with interrupted sutures, using 0.0025 black silk (Deknatel) and a 10 mm. Kalt corneal one-half circle needle, and attempting to make intracorneal or intrascleral sutures. No harmful results, however, have followed placing the sutures through and through. With a strong-toothed forceps and a firm needle holder, the outer coats of the eye can be penetrated readily with this fine needle, provided it is inserted close to the forceps fixing the tissue. The closure is not considered satisfactory unless the anterior chamber can be filled with air after the sutures are tied. The air depresses the contents of the anterior chamber away from the wound, preventing anterior synechiae. It has remained in the chamber for as long as five days. This procedure has proved to be far superior, as judged by subsequent recovery, to the frequently used method of simply fashioning a conjunctival flap over the wound without suturing the tunica fibrosa.

That low intraocular tension might be a factor in the causation of sympathetic uveitis has been considered by many observers. Samuels [20] noted that the degree of specific infiltration was usually less in glaucomatous eyes. There were, in the present series, 6 cases (cases 9, 22, 25, 28, 34 and 35), 4 being cases of hemorrhagic glaucoma, in which the tension in the exciting eye was recorded as elevated during the incubation period. In the majority of the other cases, especially those associated with injury, the tension was probably low or normal. In 5 of the 6 cases in which the tension was high there was marked sympathogenic infiltration and in 1 mild infiltration. This last eye was

18. Samuels, B.: Significance of Specific Infiltration at Site of Injury in Sympathetic Ophthalmia, Arch. Ophth. **9**:540 (April) 1933; Notes on Pathology and Surgical Treatment of Sympathetic Ophthalmia, ibid. **15**:59 (Jan.) 1936.

19. Verhoeff, F. H.: Am. J. Ophth. **19**:715, 1936.

20. Samuels, B.: Glaucoma and Sympathetic Ophthalmia, Arch. Ophth. **17**: 1031 (June) 1937.

enucleated within four weeks of the injury (case 9). Trephine operations are frequently followed by hypotension for a considerable time, and yet in this series there was only 1 instance of sympathetic ophthalmia following trephining, and in this case the trephine wound was filled with iris tissue. The possibility arises then of low tension per se being unimportant in the causation of sympathetic ophthalmia unless there is the complication of a wound poorly united because of the incarceration of intraocular tissue.

INCUBATION TIME

In this series the interval from the time of injury to the onset of sympathetic symptoms in the uninjured eye was uniform, averaging eight weeks. The shortest time was seventeen days (case 6) and the longest, forty weeks (case 29). The actual period was probably less than eight weeks if one considers the appearance of cells in the aqueous by slit lamp examination to be the first sign, for in many instances slit lamp examination was not made at the onset, and some of the histories were rather indefinite in stating time relationships. Neverthless, the time of incubation was strikingly consistent. Many patients were not seen until keratic precipitates were already present but gave a history of slight irritability for some time previous. The onset was taken to be at the first signs of irritability. In no case in this series were symptoms first noted years after injury as occasionally reported.[21] In 1 case in this series (case 11) symptoms did develop in the uninjured eye twenty-four years after a perforating injury which produced phthisis bulbi. However, this phthisic eye was struck and ruptured eight weeks before the onset of symptoms in the other eye. The later injury may have been the cause of the sympathetic reaction, or it may have excited an old latent sympathetic condition into renewed activity. In many cases, at the onset of the disease the sympathizing eye shows comparatively little irritation, which sometimes clears and recurs later. Such circumstances may explain cases in which sympathetic ophthalmia is reported to have developed years after an original injury, and the rarity of these makes such an explanation reasonable.

Regarding cases in which the incubation period is unusually short, it is noteworthy that in the 3 proved cases (6, 15 and 35) in which symptoms were evident within three weeks after injury or operation the patients were seen at the hospital at the time of injury and were

21. Schirmer, O.: Arch. f. Ophth. **38**:95, 1892. Vignaux, J. C.: De l'énucléation dans le traitement de l'ophthalmie sympathique, Thesis, Paris, no. 349, Paris, J. B. Baillière et fils, 1877. Weeks, J. E.: New York Eye & Ear Infirmary Rep. **2**:30, 1894. Knapp, H.: Arch. f. Augenh. **2**:133, 1894. Smith, J. W.: Sympathetic Ophthalmia: Report of Case Occurring Forty-Eight Years After Injury, Arch. Ophth. **2**:169 (Aug.) 1929.

under observation until symptoms developed, so that accurate details are known. In 6 cases in this series symptoms developed after enucleation of the injured eye. A summary of the data for these 6 cases follows:

	Case No.	Time From Injury to Enucleation	State of Sympathizing Eye at Time of Enucleation	Time From Enucleation to Onset of Symptoms	Final Vision
Proved cases	32	3 weeks	Normal	7 days	Lost
	9	4 weeks	Normal	7 days	20/70
	11	6 weeks	Normal	14 days	20/20
	20	13 days	Normal	28 days	20/30
Unproved cases	44	7 weeks	Normal	21 days	L. P. Cataract (?)
	49	3 weeks	Normal	7 days	20/20

Samuels [22] cited a case in which sympathetic ophthalmia developed forty-one days after enucleation. That sympathetic ophthalmia actually develops after enucleation is inconceivable, but as there were no gross signs or symptoms in the sympathizing eye at the time of enucleation, these cases emphasize the insidious onset of the disease. Verhoeff [23] has noted sympathetic infiltration in the exciting eye in a number of instances in which the clinical record stated that the fellow eye was normal, but on calling the patients back for reexamination the remaining eye showed definite descemetitis. He has, however, found 1 such case in which no symptoms ever developed in the other eye. Trowbridge [9] cited 2 similar cases.

The specific condition then does not start simultaneously in both eyes, but the evidence at present is that the transference can be made within two weeks. These cases also emphasize the fact that after the onset of symptoms in the sympathizing eye enucleation does not prevent further progress of the disease, although the outcome in 3 of the 4 proved cases might appear to indicate that early enucleation had a favorable effect were it not for the fact that in other cases, to be discussed later, in which the time between injury and enucleation was no longer than in these cases the sympathizing eyes were ultimately lost. From the foregoing consideration of the short incubation periods, enucleation must be done within two weeks of the injury if sympathetic ophthalmia is to be prevented.

CLINICAL RELATIONSHIPS OF POSSIBLE DIAGNOSTIC SIGNIFICANCE

The clinical appearance of the uveitis of sympathetic ophthalmia is well known. It has no pathognomonic characteristics; consequently, the sequence of events becomes important in establishing the clinical diagnosis. The coincident signs of activity in the two eyes were analyzed in an attempt to elaborate further diagnostic relationships. All of the

22. Samuels, B.: Tr. Am. Ophth. Soc. **30**:253, 1932.
23. Verhoeff, F. H.: Tr. Am. Ophth. Soc. **29**:302, 1931.

exciting eyes in both proved and unproved cases, where described, showed irritability at the onset of symptoms in the sympathizing eye. There were only 2 instances (cases 3 and 6) in which the records stated that the exciting eye was less inflamed than the sympathizing eye at this time, and in these there was some evidence of irritability in the exciting eye. In addition, as far as can be stated from hospital records, the disease ran parallel courses in the two eyes, with exacerbations and remissions occurring coincidentally. This finding does not necessarily mean that specific infiltration would be the same or that ultimate vision would be equally affected in both eyes, for in one eye involvement might be primarily in the posterior segment, whereas in the other eye it might be in the anterior segment.

I recently had occasion to consider this relationship in diagnosing a case in which uveitis had developed six weeks after cataract extraction in the other eye. The uveitis was characterized by mutton-fat deposits on Descemet's membrane, but the presumably exciting eye showed no evidence of activity by slit lamp examination; consequently the case was not considered to be one of sympathetic uveitis. Subsequent pathologic report proved this assumption to be correct.

The early observers noted a characteristic relationship between the clinical appearance of the sympathizing eye and that of the exciting eye, the sympathizing eye being characterized by the early presence of keratic precipitates (conglomerate clumps of cells on the posterior corneal surface, pathognomonic of posterior uveitis), whereas the exciting eye was said not to show such precipitates. In fact, if uveitis in the injured eye showed keratic precipitates, sympathetic uveitis was not expected to follow.[24] In this series records sufficiently detailed to be usable for comparing the appearance of keratic precipitates in the exciting eye with their appearance in the sympathizing eye showed that: Keratic precipitates appeared first in the sympathizing eye in 23 proved and in 14 unproved cases; they appeared simultaneously in both eyes in 3 proved (18, 21 and 25) and in 4 unproved cases (41, 43, 55 and 58), and first in the exciting eye in none of the proved cases and in 1 of the unproved cases (47).

In the unproved case a uveitis resulting in keratic precipitates was present before the operative injury occurred, exciting sympathetic ophthalmia. There is then no reasonable evidence of keratic precipitates developing in the exciting eye before they do in the sympathizing eye.

Comparison of the appearance of evidence of involvement of the posterior segment (keratic precipitates) in the sympathizing eye with the appearance of evidence of involvement of the anterior segment

24. Samuels, B.: Am. J. Ophth. **19**:493, 1936.

(anterior synechiae, Koeppe nodules and increased protein content of the aqueous [25]) in the sympathizing eye, as stated in the usable records, showed that: Involvement of the anterior segment preceded keratic precipitates in 4 proved cases (4, 28, 29 and 36) and in 2 unproved cases (47 and 51); it occurred simultaneously with keratic precipitates in 10 proved cases and in 14 unproved cases; and it followed the appearance of keratic precipitates in 16 proved cases and in 6 unproved cases.

Since keratic precipitates indicate involvement of the posterior segment, the sequence of their appearance then indicates that the specific condition always involves the posterior segment of the sympathizing eye before, or coincidentally with, involvement of the posterior segment of the exciting eye and that the posterior segment of the sympathizing eye with few exceptions is involved simultaneously with or before the anterior segment of this eye.

The foregoing relationships suggest that the course of the sympathetic ophthalmia runs somewhat as follows: Specific infiltration in the exciting eye in the region of the wound,[22] which is usually in the anterior segment, resulting in plastic inflammation in this eye; subsequent transference of the disease to the posterior segment of the sympathizing eye, as judged by the early appearance of keratic precipitates in this eye; almost simultaneous anterior involvement of the sympathizing eye, as judged by the formation of synechiae, increased aqueous flare and Koeppe nodules, and almost coincident posterior involvement of the activating eye, as judged by the appearance of keratic precipitates in this eye. These clinical observations may give an apparent rather than an actual progression, since the picture in the activating eye may be obscured by the sequela of the injury. Nevertheless, if further series of cases establish that this course is typical, it may prove to be of diagnostic importance. For instance, uveitis occurring in one eye subsequent to injury in or operation on the fellow eye would be less likely, by a 1 to 10 chance, to be sympathetic uveitis if at the onset there was no involvement of the posterior segment, as judged by the absence of keratic precipitates. Similarly, bilateral uveitis following operation on both eyes at about the same time might well be sympathetic ophthalmia if one of the eyes showed keratic precipitates early in the disease while the other did not. In this example the eye with keratic precipitates would more likely be the sympathizing eye.

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25. In collaboration with A. R. Irvine (Proceedings of Pan Pacific Surgical Congress, Honolulu, 1939), I showed that in other types of uveitis dense keratic precipitates may be present in an eye having normal aqueous protein and no synechiae in the iris. The protein content of the aqueous becomes increased with involvement of the anterior segment, and synechiae vary proportionately with the protein content and the length of time it has been increased.

COURSE OF THE DISEASE

Once developed, the course of the disease is that of a low grade uveitis with exacerbations and remissions, gradually subsiding in about half the cases and progressing to phthisis bulbi or glaucoma with loss of useful vision in the other half, as seen in the accompanying synopsis: Among the cases in which useful vision was retained there were 13 proved and 8 unproved cases in which the disease was inactive and 10 proved and 6 unproved in which it was considered still active; while among the cases in which the eyes were hopelessly blind there were 13 proved and 12 unproved cases. The disease was considered inactive if there had been no exacerbation within a year, except in cases 19 and 47, in which it was inactive nine and ten months but active only two and three months, respectively. In no case in which the disease was considered inactive and the final results were good had there been more than two exacerbations or signs of activity for over a year, whereas in the cases in which the results were bad the course was much more chronic and the exacerbations were roughly proportionate to the length of time the cases were followed. One of the proved cases in which the disease was still active (case 16) is especially interesting, the patient having had about one exacerbation a year for eight and one-half years and still retaining vision of 20/30. In another case in this group (17), after nine years of inactivity there was a recurrence, the disease being slightly active when the patient was last seen, but vision remained 20/30. These cases demonstrate the chronicity of the disease and the possibility of a flare-up even after a long period of inactivity. Involvement of the choroid, slight to moderate cyclitis, opacities in the vitreous, and keratic precipitates can continue for years without loss of useful vision (proved cases 12, 15, 16 and 17 and unproved cases 40, 43, 62 and 63), whereas primary involvement of the anterior segment with iritis, adhesions and pupillary membrane produces glaucoma, which is usually hopeless and only made worse by operation.

The advisability of operative procedures on the sympathizing eye after the development of the uveitis was discussed in a previous paper.[2] In summary, of 16 cases in which operation was done, it was performed in 14 while there were still signs of activity and in 2 after a period of inactivity. The final results were good in the last 2 cases. Of the other 14, there were good final results in only 4, in 3 of which treatment with diphtheria antitoxin was given before and after operation. The poor results emphasize the well known axiom that elective operations should be put off as long as possible after activity has ceased.

Regarding the course of the disease in children, the prevalent impression is that the prognosis for children is poorer than for adults. Statistically, this impression was not confirmed by the cases in the present

series, in which the outcome for children was as follows: useful vision in 4 proved and in 5 unproved cases and loss of useful vision in 3 proved and in 6 unproved cases.

EFFECT OF ENUCLEATION

The effect of enucleation of the exciting eye on the course of the disease in the sympathizing eye, once the condition had been established, was not a positive one in this series of cases. Many of the histories recorded an immediate beneficial result on the sympathizing eye after enucleation. However, in 6 there was no change and in 2 others the sympathizing eye was said to be worse. In addition, the majority of the patients had exacerbations of the disease at some time after enucleation, nullifying the evidence of apparent benefit. The immediate good response might be explained easily by the rest and intensive treatment during hospitalization for enucleation and not by the enucleation itself.

Omitting cases in which the disease was still active, analysis of final results reveals:

Of 14 cases in which results were poor, enucleation was not done in 3, enucleation was done years after injury in 3 and enucleation was done on the average of ten weeks after injury in 8 (in 4 of these the time interval was under ten weeks, the shortest period being three weeks).

In 13 cases in which the final results were good the time between injury and enucleation averaged ten weeks (in 7 it was under ten weeks, the longest interval being sixteen weeks).

The apparently beneficial effect of enucleation suggested in the analysis is counterbalanced, however, if unproved cases are included. In many of these the exciting eye was never removed, and a fair comparison can be obtained only by including cases in which enucleation was not done.

The visual results in 17 cases in which enucleation was not done and in 42 in which it was carried out are summarized as follows:

	No. of Cases	Visual Result, Percentage		
		Good	Useful	Useless
No enucleation	17	41	12	47
Enucleation	42	45	10	45
(a) Before sympathetic symptoms	8	50	12	38
(b) Within ten days after sympathetic symptoms	20	45	15	40

The results in the two groups are so similar that enucleation cannot be said to lessen the severity of the disease or to shorten its course appreciably once it has started. In the group with good results, as in the group with poor results, there are both extremes, some of the longest and some of the shortest intervals between injury and enucleation being in each group. This same lack of correlation of effect of enucleation

on the course of the disease was seen in analysis of the time relationships in the series of 35 cases reported by Fuchs [10g] and is in contrast to the results recently reported by Trowbridge [9] and Joy.[26] The exciting eye apparently does not act as a focus of infection "spilling over" into the sympathizing eye, as judged by the exceptional instances of 6 cases (1, 6, 7, 10, 19 and 22) in which there was "severe" sympathogenic infiltration but good vision was retained, cure being recorded, and 2 cases (29 and 33) in which there was "mild" sympathogenic infiltration and useful vision was lost.

In the 3 last cases the eyes were retained long enough to have developed marked infiltration, as judged by comparison with the 6 first-mentioned cases. What correlation there is between the two eyes in the course of the disease as previously discussed is probably the result of the general powers of resistance of the patient affecting both eyes rather than an effect of one eye on the other. Of course, if the exciting eye is hopelessly blind there could be no argument against enucleation, but if it has useful vision it might better be retained, as there might be instances in which the ultimate outcome would be better in the exciting than in the sympathizing eye. This possibility is especially true in cases in which operation is performed, since the exciting eye is usually not severely damaged. In case 13, for example, sympathetic uveitis developed following cataract extraction, and the vision was finally 20/50 in the exciting eye with only 20/200 in the sympathizing eye.

FINAL VISUAL RESULTS

Without consideration of treatment, the final visual results in cases of sympathetic ophthalmia are surprisingly alike in all series reported in the literature, useful vision being retained in approximately 50 per cent and the condition progressing to loss of useful vision in 50 per cent. In the series reported by Fuchs [10g] in 1905, good results were obtained in 45 per cent of 33 cases and poor results in 34 per cent. Morax,[27] discussing 39 cases of war injuries, reported good results in 53 per cent, fair results in 3 per cent and poor results in 34 per cent. In Post's [28] series of 25 cases reported in 1934, normal vision was retained in 52 per cent and useful vision was lost in 44 per cent. Results in the present series, excluding cases in which the disease was still active, are summarized as folows:

	Visual Result, Percentage		
	Good	Useful	Useless
Total (59 cases)	44	10	45
After injury (37 cases)	46	5	49
After operation (22 cases)	41	14	45

26. Joy, H. H.: Prognosis of Postoperative Sympathetic Ophthalmia: Statistical Study, Arch. Ophth. **17**:677 (April) 1937.

27. Morax, V.: Ann. d'ocul. **154**:426, 1917.

28. Post, L. T.: South. M. J. **27**:421, 1934.

As shown in the previous paper [2] dealing with the results of treatment with diphtheria antitoxin, the percentage of good results was definitely higher in the series of cases in which intensive treatment was given before the disease had progressed to an advanced stage.

CONCLUSIONS AND SUMMARY

The following conclusions are suggested from review of the 63 cases presented:

In this series there is no instance of sympathetic ophthalmia developing without perforation of the globe.

If enucleation is to prevent the development of sympathetic uveitis, it must be done before two weeks have elapsed from the time of injury.

Once sympathetic uveitis has developed, enucleation of the exciting eye has no effect on the course of the disease, and this eye should be retained, if potentially useful, as it may eventually be the better eye. From the available data there is no indication that the exciting eye acts as a focus of infection "spilling over" into the sympathizing eye.

Considering the frequency of occurrence of sympathtic ophthalmia, 1 per cent of all perforating injuries, attempts to save severely damaged eyes, especially if the lens is injured, are not justified if the fellow eye is normal. A distinct possibility of sympathetic uveitis must be considered when operation is contemplated on eyes nearly blind from any cause, as for instance, hemorrhagic glaucoma.

The progression of symptoms in the course of the disease may be of diagnostic importance: (*a*) The exciting eye is always irritable at the onset of symptoms in the sympathizing eye. (*b*) Keratic precipitates are nearly always present in the sympathizing eye and make their appearance in this eye before they appear in the exciting eye. Uveitis developing about six weeks after injury or operation to the fellow eye, showing at the onset no keratic precipitates, has about a 10:1 probability of not being sympathetic uveitis.

The wounds exciting sympathetic uveitis, whether traumatic or operative, characteristically show incarcerated lens substance or uveal tissue. This fact and the incidence of the condition after various types of operations suggest that iris inclusion operations are more likely to cause complications with sympathetic uveitis than trephine operations; they further suggest that repair of perforating injuries should include freeing the wound of incarcerated substance and firmly uniting the tunica fibrosa. A method to accomplish this end is included.

DETERMINATION AND SIGNIFICANCE OF THE PHOTOPIC RETINAL VISIBILITY CURVE

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The purpose of the present paper is to describe the transformation of a photopic ocular visibility curve into a photopic retinal visibility curve by applying suitable corrections for the absorption and reflection of light by the ocular media of the human eye. An examination of the photopic retinal visibility curve thus attained permits certain tentative conclusions to be drawn concerning the nature of the visual process at relatively high intensities of illumination.

The relative sensitivity of the human eye to light of different wavelengths at relatively high levels of illumination has been the subject of numerous investigations.[1] The results of these experiments may be expressed in terms of "visibility" or "luminosity" curves. An ocular visibility curve is determined by finding, for different wavelengths of light, the amount of energy to which the eye must be subjected in order to produce a given sensation of brightness. From determinations made while the eye is light adapted one obtains the photopic ocular visibility curve, while if the eye is dark adapted the scotopic ocular visibility curve is found. As is well known, such determinations show that relatively large amounts of energy are required to produce a given brightness sensation when the wavelength employed is near the extremes of the visible spectrum, while relatively little energy is necessary to produce an appearance of equal brightness if the wavelength used is near the middle of the visible spectrum. This means, of course, that the visual mechanism is less sensitive to the blue and red portions of the spectrum than it is to the yellow and green portions. If the reciprocal of the energy necessary to produce a given sensation of brightness is plotted as a function of wavelength, there results a visibility curve which indicates the sensitivity

From the Howe Laboratory of Ophthalmology, Harvard University, and the Massachusetts Eye and Ear Infirmary.

1. (*a*) König, A.: Ueber den Helligkeitswerthe der Spektralfarben bei verschiedener absoluter Intensität, Beitr. z. Psychol. u. Physiol. d. Sinnesorg., 1891, p. 309. (*b*) Reeves, P. R.: The Visibility of Radiation, Tr. Illum. Engin. Soc. **13** (pt. 2):101, 1918. (*c*) Laurens, H.: Studies on the Relative Physiological Values of Spectral Lights: IV. The Visibility of Radiant Energy, Am. J. Physiol. **67**:348, 1924. (*d*) Sloan, L.: The Effect of Intensity of Light, State of Adaptation of the Eye, and Size of Photometric Field on the Visibility Curve, Psychological Monograph, Princeton, N. J., Psychological Review Co., 1938, vol. 38, p. 1.

of the eye to light of various wavelengths. The various photopic ocular visibility curves which have been published are all similar, and that adopted as standard by the International Commission on Illumination is reproduced in chart 3. These curves do not indicate the sensitivity of the retina, however, because allowance has not been made for selective reflection and absorption of light by the ocular media. Making such an allowance might change the appearance of the photopic visibility curve, since it markedly alters the scotopic visibility curve. Thus in chart 1 the dash line is a scotopic luminosity curve as determined by Hecht and Williams,[2] while the solid line represents the data of Hecht and Williams, which have been corrected for reflection and absorption by the ocular media so as to permit conclusions as to retinal sensitivity. The solid line curve is a scotopic *retinal* visibility curve, while the dash line

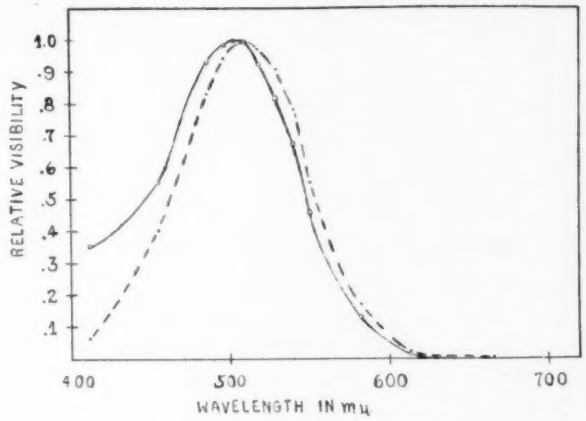

Chart 1.—The dash line is the scotopic ocular visibility curve in terms of energies (Hecht and Williams); the solid line, the scotopic retinal visibility curve (Ludvigh).

curve is a scotopic *ocular* visibility curve. The former curve agrees reasonably well with the absorption spectrum of rhodopsin as determined by Krause and Sidwell [3] and by Lythgoe,[4] while the latter curve does not. The method used to determine the absorption of the ocular media has been described in a previous paper in the ARCHIVES.[5] The transformation

2. Hecht, S., and Williams, R. E.: The Visibility of Monochromatic Radiation and the Absorption Spectrum of Visual Purple, J. Gen. Physiol. **5**:1, 1922.

3. Krause, A. C., and Sidwell, A. E.: The Absorption Spectra of Visual Purple and Its Photodecomposition Products, Am. J. Physiol. **121**:215, 1938.

4. Lythgoe, R. J.: The Absorption Spectra of Visual Purple and of Indicator Yellow, J. Physiol. **89**:331, 1937.

5. Ludvigh, E., and McCarthy, E. F.: Absorption of Visible Light by the Refractive Media of the Human Eye, Arch. Ophth. **20**:37 (July) 1938.

of a scotopic ocular visibility curve into a scotopic retinal visibility curve and the resulting agreement with the absorption spectrum of rhodopsin has also been discussed in the ARCHIVES.[6]

In the present paper the photopic ocular visibility curve will be transformed into a photopic retinal visibility curve by applying suitable corrections for the absorption of light by the ocular media. The photopic ocular visibility curve selected for this treatment is that advocated by Gibson and Tyndall [7] and adopted as standard by the International Commission on Illumination.[8] Gibson and Tyndall made use of the data of Coblentz and Emerson,[9] Hyde, Forsythe and Cady,[10] Ives [11] and Nutting,[12] as well as their own, in arriving at their standard visibility curve.

ABSORPTION OF LIGHT BY MACULA LUTEA

The size of stimulus field used by these observers was such as to subtend the following angles at the nodal points of the eyes examined: Coblentz and Emerson, 2 degrees; Ives, 2 degrees; Nutting, 2 degrees; Gibson and Tyndall, 3 degrees. It is therefore clear that with foveal fixation the stimulus falls on the macula lutea area. Gullstrand [13] expressed the belief that the macular portion of the retina is not differentially pigmented during life. Nordenson and Nordmark [14] agreed partially with Gullstrand. The consensus is, however, that a yellow pig-

6. Ludvigh, E.: Determination and Significance of the Scotopic Retinal Visibility Curve, Arch. Ophth. **20**:713 (Nov.) 1938.

7. Gibson, K. S., and Tyndall, E. P. T.: Visibility of Radiant Energy, Scientific Paper 475, United States Department of Commerce, Bureau of Standards, 1923-1924, p. 131.

8. International Commission on Illumination, Proceedings, Sixth Meeting, Geneva, Switzerland, July 1924, Cambridge, England, 1926, pp. 67 and 232.

9. Coblentz, W. W., and Emerson, W. B.: Relative Sensibility of the Average Eye to Light of Different Colors and Some Practical Applications to Radiation Problems, Scientific Paper 303, United States Department of Commerce, Bureau of Standards, 1917, p. 167.

10. Hyde, E. P.; Forsythe, W. E., and Cady, F. E.: The Visibility of Radiation, Astrophys. J. **48**:65, 1918.

11. Ives, H. E.: Studies in the Photometry of Lights of Different Colours, Phil. Mag. **24**:149, 1912.

12. Nutting, P. G.: (*a*) The Visibility of Radiation, Phil. Mag. **29**:301, 1915; (*b*) 1919 Report of the Standards Committee on Visual Sensitometry, J. Optic. Soc. America **4**:55, 1920.

13. Gullstrand, A.: (*a*) Die Farbe der Macula centralis retinae, Arch. f. Ophth. **62**:1, 1906; (*b*) Zur Maculafrage, ibid. **66**:141, 1907; (*c*) Die Macula centralis im rotfreien Lichte, Klin. Monatsbl. f. Augenh. **60**:289, 1918.

14. Nordenson, J. W., and Nordmark, T.: Bemerkung zur Frage über die Farbe der Macula lutea, Upsala läkaref. förh. **33**:499, 1927.

ment is present in the cerebral layers of the retina during life.[15] Since the macular pigment is believed to be confined to the cerebral layers of the retina,[16] it may be that in those portions of the fovea where the cerebral retinal layers are absent the yellow pigmentation is lacking. The foveolus, however, subtends considerably less than 1 degree at the nodal point of the eye [17] and constitutes only about 10 per cent of the total area of the subject's retina stimulated during the experiments on which the International Commission on Illumination visibility curve is based. If it is assumed that the foveolus lacks pigmentation, an attempt could be made to allow for this local absence of pigment. The calculation involved would be somewhat dubious, however, since the relative functional importance of the foveolus as compared to the entire macula is difficult to estimate. It seems more practical, as a first approximation, to assume that the entire fovea possesses an evenly distributed yellow pigment. In this case full allowance must be made for the absorption of the yellow pigment.

Determinations of the absorption spectrum of the pigment of the macula lutea have been made by Sachs,[18] Kohlrausch [19] and Kravkov.[20] Although it is difficult to make these determinations with extreme accuracy, nevertheless it is natural to believe that a more adequate notion

15. (*a*) Schmidt-Rimpler, H.: Die Farbe der Macula lutea, Arch. f. Ophth. **57**: 24, 1904. (*b*) Chevallereau, A., and Polack, A.: De la coloration jaune de la macula, Ann. d'ocul. **138**:241, 1907. (*c*) Dimmer, F.: Die Macula lutea der menschlichen Netzhaut und die durch sie bedingten entoptischen Erscheinungen, Arch. f. Ophth. **65**:486, 1907. (*d*) van der Hoeve, J.: Die Farbe der Macula lutea, ibid. **80**:132, 1912. (*e*) Vogt, A.: Herstellung eines gelbblauen Lichtfiltrates, in welchem die Macula centralis in vivo in gelber Färbung erscheint, die Nervenfasern der Netzhaut und andere feine Einzelheiten derselben sichtbar werden, und der Grad der Gelbfärbung der Linse ophthalmoskopisch nachweisbar ist, ibid. **84**:293, 1913; (*f*) Ophthalmoskopische Untersuchungen der Macula lutea im rotfreien Licht, Klin. Monatsbl. f. Augenh. **66**:321, 1921. (*g*) Holm, E.: Das gelbe Maculapigment und seine optische Bedeutung, Arch. f. Ophth. **108**:1, 1922.

16. (*a*) Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1934, vol. 1, p. 95. (*b*) Kolmer, W.: Die Netzhaut (Retina), in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1936, vol. 3, pt. 2, p. 376.

17. (*a*) Dimmer, F.: Beiträge zur Anatomie und Physiologie der Macula lutea des Menschen, Leipzig, Franz Deuticke, 1894. (*b*) Rochon-Duvignaud, A.: Recherches sur la fovea de la rétine humaine et particuliairement sur le bouquet de cônes centraux, Arch. d'anat. micr. **11**:315, 1907.

18. Sachs, M.: Ueber die spezifische Lichtabsorption des gelben Fleckes der Netzhaut, Arch. f. d. ges. Physiol. **50**:574, 1892.

19. Kohlrausch, A.: Tagessehen, Dämmerungssehen, Adaptation, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 12, pt. 2, p. 1516.

20. Kravkov, S. W.: Ueber die Lichtabsorption im gelben Flecke des lebenden Auges, Arch. f. d. ges. Physiol. **210**:781, 1925.

of the sensitivity of the retina can be obtained if allowance is made for absorption by the macula lutea than is available if this correction is totally neglected. The observations of Sachs, Kohlrausch and Kravkov were not all made at the same wavelengths. In order to average the results of these authors, Lagrange's interpolation formula was applied so as to determine the absorption of each individual macula at 10 millimicron wavelength intervals throughout the visibile spectrum. The results at each wavelength for all the maculas were then averaged.

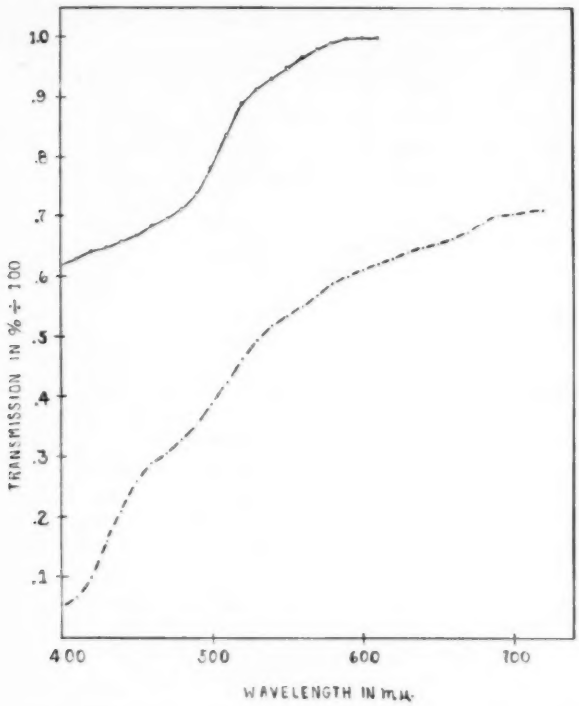

Chart 2.—The solid line indicates the transmission of light of various wavelengths by the macula lutea; the dash line, the transmission of the macula lutea and the refractive media of the eye (Ludvigh).

The transmission of light of various wavelengths by the macula lutea is indicated by the solid line in chart 2.

DETERMINATION OF PHOTOPIC RETINAL VISIBILITY CURVE

Allowance must also be made for losses of light occurring in the ocular media. By combining the data of Sachs, Kohlrausch and Kravkov with those of Ludvigh and McCarthy,[5] the total transmission of the ocular media and the macula lutea has been computed and is indicated

by the dash line in chart 2. It can be observed that in passing from the red to the blue end of the spectrum a smaller and smaller fraction of the energy incident on the cornea reaches the bacillary layer of the retina. When allowance is made for the combined transmission of the ocular media and the macula lutea, the photopic ocular visibility curve is transformed to a photopic retinal visibility curve, as is illustrated in chart 3.

In chart 3 the dash line curve is the photopic ocular visibility curve adopted as standard by the International Commission on Illumination. It is based on the results obtained by the examination of the eyes of approximately 200 persons. The solid line shows the photopic retinal visibility curve which is obtained when allowance is made for intraocular

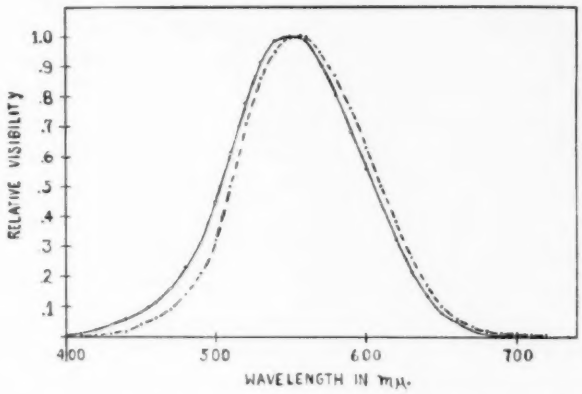

Chart 3.—The dash line is the Illumination Engineering Society's photopic ocular visibility curve in energy terms (Gibson and Tyndall); the solid line, the corresponding photopic retinal visibility curve (Ludvigh).

absorption. The latter curve is more symmetric than the former and its maximum is shifted toward the short wavelength end of the visible spectrum. The maximum of the photopic ocular visibility curve is at 555 millimicrons, while that of the photopic retinal visibility curve as determined by fitting to a three term Fourier series is at 549.6 millimicrons. The difference between the two maxima is thus 5.4 millimicrons. Hecht and Williams [2] have stated that a correction of the data of Hyde, Forsythe and Cady [10] for the data of Sachs [18] for the macula lutea produces a shift of the maximum of 14 millimicrons. Hecht and Williams, however, made no allowance for the absorption of the refractive media of the eye, and in any case, as has been pointed out by Laurens,[1c] their calculation is in error.

PHOTOSENSITIVE SUBSTANCES ASSOCIATED WITH RETINAL CONES

The question now arises: What is the explanation of the shape of the photopic retinal visibility curve? As has been noted, the shape of the scotopic retinal visibility curve resembles rather closely that of the absorption spectrum of rhodopsin. But no photosensitive substance with an absorption spectrum corresponding to the photopic retinal visibility curve has been found. Von Studnitz [21] has indeed reported the presence of a photosensitive substance in the cone type of retina of the turtle, Testudo graeca, but the variation with wavelength of the absorption coefficient of this substance is unlike the variation with wavelength of the sensitivity of the eye. Wald [22] has extracted from the mixed rod and cone type of retina of chickens a substance which he has named iodopsin. Irradiation of this substance with extreme red light of wavelengths above 650 millimicrons results in a change in its absorption spectrum. The difference between the absorption spectrum before and after such irradiation is termed a "difference spectrum." The maximum of this difference spectrum occurs at about 580 millimicrons, which is in agreement with Honigmann's [23] determination of the maximum of the visibility curve of light-adapted chickens. As Wald pointed out, however, the difference spectrum is not the absorption spectrum. In the critical blue region the difference spectrum is negative, and Honigmann's observations on light-adapted chickens did not extend below 500 millimicrons. The degree of agreement in this blue region is, therefore, quite unknown. The presence of droplets of colored oil in the chicken retina [24] also confuses the issue.

Bayliss, Lythgoe and Tansley [25] have reported that the absorption maximum of visual purple may vary between 505 and 545 millimicrons in different species of fish and between 525 and 535 millimicrons in the same species. These differences are not, however, correlated with the rod or cone type of retina, and two maxima are not observed in the same

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21. von Studnitz, G.: (*a*) Ueber die Lichtabsorption der Retina und die photosensiblen Substanzen der Stäbchen und Zapfen, Arch. f. d. ges. Physiol. **230**:614, 1932; (*b*) Weitere Studien an der Zapfensubstanz, ibid. **239**:515, 1937.

22. Wald, G.: Photo-Labile Pigments of the Chicken Retina, Nature, London **140**:545, 1937.

23. Honigmann, H.: Untersuchungen über Lichtempfindlichkeit und Adaptierung des Vogelauges, Arch. f. d. ges. Physiol. **189**:1, 1921.

24. (*a*) Kühne, W., and Ayres, W.: On the Stable Colors of the Retina, J. Physiol. **1**:109, 1878. (*b*) Waelchli, G.: Mikrospektroskopische Untersuchungen der gefärbten Kugeln in der Retina von Vögeln, Arch. f. Ophth. (pt. 2) **27**:303, 1881. (*c*) Wald, G., and Zussman, H.: Carotenoids of the Chicken Retina, J. Biol. Chem. **122**:449, 1938.

25. Bayliss, L. E.; Lythgoe, R. J., and Tansley, K.: Some New Forms of Visual Purple Found in Sea Fishes, with a Note on the Visual Cells of Origin, Proc. Roy. Soc., London, s.B **120**:95, 1936.

fish. Furthermore, these variations may not occur in visual purple of mammalian retina, and indeed in the rat the individual differences in the wavelength of maximum absorption of visual purple are negligible. It thus appears that the various species of fish examined do not possess any photosensitive substance capable of explaining, even by analogy, the characteristics of the photopic retinal visibility curve.

Adams [26] has suggested the possibility that several cone substances may exist. He stated that "compounds of closely related chemical composition may differ in color sufficiently to account for the sensation curves for human vision." He pointed out that the wavelength of maximum absorption of crystal violet, or hexamethylpararosaniline, salts varies from 450 to 630 millimicrons, depending on the number of hydro-

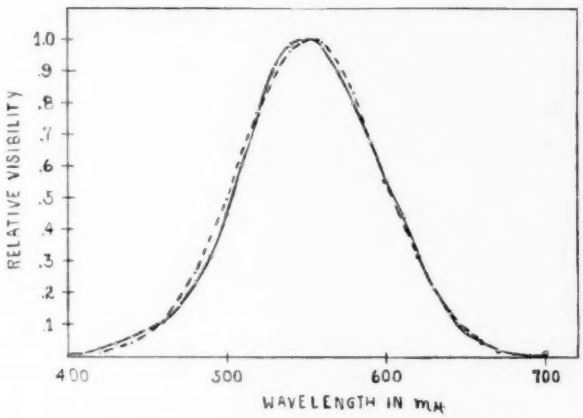

Chart 4.—The solid line is the photopic retinal visibility curve; the dash line, a graph of the equation $V = e^{-0.000253\ (552.6 - \lambda)^2}$.

chloric acid molecules added, and suggested that the difference between the red, green and blue "excitation" curves may be dependent on similar relatively slight chemical modifications of a single photosensitive substance. It is noticeable, however, that all the absorption spectrums depicted are markedly asymmetric. One may conclude that no photosensitive substance so far found in animal eyes possesses an absorption spectrum shown to correspond to the photopic retinal visibility curve.

If a photosensitive substance mediating photopic vision were found, one might expect its absorption spectrum to correspond to the photopic retinal visibility curve. Indeed, it would seem possible that the photopic retinal visibility curve might provide a more accurate indication of the absorption spectrum of the assumed photosensitive material than would be provided if the material were extracted from the retina and subjected

26. Adams, E. Q.: A Theory of Color Vision, Psychol. Rev. **30**:56, 1923.

to spectroscopic analysis. In the latter instance it might be difficult to eliminate all nonphotosensitive impurities [27] and to maintain the normal p_H [4] and temperature [28] of the substance in situ, factors which are known to affect the bleaching of rhodopsin.

SUGGESTED EXPLANATIONS OF SHAPE OF VISIBILITY CURVE

In chart 4 the solid line is the photopic retinal visibility curve, while the dash line is a curve determined by means of the equation $V = e^{-0.000253\ (552.6 - \lambda)^2}$. This is a simple form of probability expression, the degenerate form, type III, of Pearson's generalized frequency distributions.[29] This simple probability expression provides a better fit for the photopic retinal visibility curve than Gibson and Tyndall's [30] four term formula does for the photopic ocular visibility curve. The criterion of "goodness of fit" applied was the average of the absolute deviations of the calculated from the observed values expressed as a percentage of the observed values. It is possible that the similarity between the curves in chart 4 would be greater if data were available on which to base a probably slight correction for fluorescence in the ocular media.

That visibility curves are similar in general appearance to probability curves has been noted.[31] But when proper allowance is made for the absorption of the ocular media, it is found that although the scotopic retinal visibility curve is skewed and corresponds to the absorption spectrum of rhodopsin, the photopic retinal visibility curve is quite symmetric and does not correspond to the absorption spectrum of any photosensitive substance so far reported.

Some attempts have been made to account for the shape of the photopic ocular visibility curve. Thus Goodeve [32] has pointed out:

> . . . the relative luminosity falls off exponentially with decreasing frequency, the curve of the logarithm of the relative luminosity against frequency being a straight line over a very wide range of values. The similarity between the shape of this curve and those of the extinction (absorption) coefficients of almost all known

27. Ludvigh, E.: Scotopic Luminosity Curve and the Absorption Spectrum of Visual Purple, Nature, London **141**:1141, 1938.

28. Dartnall, H. J. K.; Goodeve, C. F., and Lythgoe, R. J.: The Effect of Temperature on the Photochemical Bleaching of Visual Purple Solutions, Proc. Roy. Soc., London, s.B **136**:35, 1937.

29. Fry, T. C.: Probability and Its Engineering Uses, New York, D. Van Nostrand Company, Inc., 1928, p. 247.

30. Tyndall, E. P. T., and Gibson, K. S.: Visibility of Radiant Energy Equation, J. Optic. Soc. America **9**:403, 1924.

31. (*a*) Nutting.[12b] (*b*) Troland, L.: The Retinal Visibility Function, Abstr.-Bull. Phys. Lab. Nat. Electric Lamp A. **1**:378, 1913. (*c*) Hecht and Williams.[2]

32. Goodeve, C. F.: Relative Luminosity in the Extreme Red, Proc. Roy. Soc., London, s.A **155**:664, 1936.

substances which absorb light in a purely continuous manner is very marked and may be considered to lend support to the contention that the primary process of chromatic vision is the absorption of light by a coloured substance present in the retina, resulting in a photochemical change.

But it must be noted that this linear relation between log luminosity and frequency holds only for wavelengths longer than 700 millimicrons in the extreme red portion of the spectrum and fails when the visually important region of the spectrum is approached. Furthermore, an examination of the absorption spectrums of numerous substances [33] reveals that the relationship noted by Goodeve appears to be mainly true for ultraviolet rather than for visible absorption spectrums.

The photopic ocular visibility curve can be compounded with varying degrees of accuracy by adding two,[34] three [35] or more "chromatic excitation curves." These chromatic excitation curves in the form of tristimulus values are useful for the practical specification of color values in physical terms, and such specification has become standardized; [36] however, the various chromatic excitation curves themselves do not correspond to the absorption spectrum of any photosensitive retinal substance so far reported. Furthermore, it seems unlikely that two or three different absorption spectrums would result in a combined absorption spectrum as symmetric as the photopic retinal visibility curve. Troland [37] has suggested the possibility that the three chromatic excitation curves may each resemble the visibility curve and overlap almost completely in the spectrum. Hecht [38] has adopted this conception and has calculated

33. Washburn, E. W.: International Critical Tables of Numerical Data, Physics, Chemistry and Technology, prepared by the National Research Council, New York, McGraw-Hill Book Company, 1929, vol. 5, pp. 361-379.

34. Judd, D. B.: (*a*) The Mixture Data Embodied in the Tentative Curves of Hecht's Theory of Vision, J. Optic. Soc. America **20**:647, 1930; (*b*) Sensibility to Color Change Determined from the Visual Response Functions: Extension to Complete and Partial Dichromasy, abstracted, ibid. **16**:115, 1928.

35. (*a*) Maxwell, J. C.: On the Theory of Compound Colours, and the Relations of the Colours of the Spectrum, Phil. Tr. Roy. Soc., London **150**:57, 1860. (*b*) König, A., and Dieterici, C.: Die Grundempfindungen in normalen und anomalen Farbensystemen und ihre Intensitätsverteilung im Spektrum, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. **4**:241, 1892. (*c*) Abney, W.: Researches in Colour Vision and the Trichromatic Theory, London, Longmans, Green & Company, 1913. (*d*) Wright, W. D.: A Re-Determination of the Trichromatic Coefficients of the Spectral Colours, Tr. Optic. Soc. London **30**:141, 1929. (*e*) Guild, J.: The Colorimetric Properties of the Spectrum, Phil. Tr. Roy. Soc., London, s.A **230**: 149, 1931.

36. Hardy, A. C.: Handbook of Colorimetry, Cambridge, Mass., The Technology Press, 1936.

37. Troland, L. T.: Brilliance and Chroma in Relation to Zone Theories of Vision, J. Optic. Soc. America **6**:3, 1922.

38. Hecht, S.: Development of Thomas Young's Theory of Color Vision, J. Optic. Soc. America **20**:231, 1930.

extensively overlapping chromatic excitation curves which summate to give the photopic ocular visibility curve. On this view the phenomena of color mixture, hue discrimination and least perceptible colorimetric purity now become dependent on slight differences between the individual chromatic excitation curves, that is, on slight differences in the absorption spectrums of three assumed photosensitive substances.[39] Judd [34a] has pointed out that the particular chromatic excitation curves selected by Hecht are inadequate for the description of experimental data on color mixture. Furthermore, no retinal excitation curves could be expected to describe any of the experimental data on human beings dealt with by Hecht, since no allowance was made for selective absorption of light by the refractive media of the human eye. But more important than the question of the effectiveness of Hecht's attempted specific interpretation of Troland's suggestion is the problem of whether or not any general solution along these lines can be expected. Since on this view the three retinal chromatic excitation functions must summate to give the photopic retinal visibility curve rather than the photopic ocular visibility curve, it appears that the individual chromatic excitation curves will be still more symmetric and more similar to each other than those depicted by Hecht. This in turn indicates that the phenomena of color mixture, hue discrimination and least perceptible colorimetric purity would depend on still slighter individual differences between the chromatic excitation curves than those assumed by Hecht and makes the entire hypothesis less tenable.

OTHER POSSIBLE EXPLANATIONS OF SHAPE OF VISIBILITY CURVE

The symmetry and smoothness of the photopic retinal visibility curve suggest that its shape is due to the operation of either a single process or a large number of processes rather than to the operation of three or four processes. If the process in question is photochemical, it is possible that the shape of the photopic retinal visibility curve results from a single broadened absorption line in the spectrum of a retinal substance. The mechanisms involved in the broadening of an absorption line have not been thoroughly investigated, but more is known about the broadening in the reverse process of emission. The investigations have concerned mainly the gaseous state. The known causes [40] of broadening of a spectral line are the Doppler effect, natural breadth, collision damping, pressure shift and the Stark effect. Some of these broadening effects give rise to emission curves, which are symmetric when plotted against frequency but are asymmetric when plotted against

39. Hecht, S.: The Retinal Processes Concerned with Visual Acuity and Color Vision, Bulletin 4, Cambridge, Mass., Howe Laboratory of Ophthalmology, 1931, p. 48.

40. White, H. E.: The Breadth of Spectrum Lines, in Introduction to Atomic Spectra, New York, McGraw-Hill Book Company, 1934, chap. 21.

wavelength. Furthermore, the general physical conditions under which the visual process operates are not such as to lend weight to the view that such effects are of prime importance in the explanation of the photopic retinal visibility curve. Thus strong magnetic fields necessary for the production of a marked Stark effect are not known to exist in the eye, nor are the pressures there present sufficient to produce appreciable pressure broadening. In order for the Doppler effect to produce a broadening of 400 millimicrons, the approximate range of the photopic retinal visibility curve, it would be necessary that some of the light-absorbing material have a velocity approximately one-quarter as great as that of light.

Somewhat more plausible is the intriguing possibility that the broadening of the visibility curve is in some way dependent on the finite life period of whatever elements are involved in the initial process of absorption. The orthodox view [41] of the process of absorption is based on the concept that the absorbing element passes from one energy state or level, E_1, to another state, E_2, while absorbing a quantum of energy, $h\nu$. One thus has $E_2 - E_1 = h\nu$ in which h is Planck's constant and ν is the frequency of light absorbed, which is determined by the relation $\nu = \frac{E_2 - E_1}{h}$. Thus in making the transition from E_1 to E_2, only one specific frequency could be absorbed. But according to Heisenberg's [42] uncertainty principle, the energy level E_1 cannot be precisely determined unless the element involved exists for an infinite period of time. If the life period of this energy level is t, then there will be an uncertainty ΔE in the energy level E_1, such that $\Delta E = \frac{h}{t}$. Corresponding to this uncertainty in the energy level, there is an uncertainty $\Delta \nu$ in the frequency of the light which can be absorbed by the element during its transition from one state to the other. This produces a broadening of the absorption spectrum. The amount and character of the broadening are dependent on the distribution of life periods in the population of absorbing elements. But no matter what the population distribution assumed, the broadened spectrum is symmetric only if plotted on a frequency scale. It therefore appears that broadening due to the finite life period of the absorbing elements will not account for the shape of the photopic retinal visibility curve.

It is possible that the initial process in high intensity vision is a photoelectric rather than a photochemical one. In this case the shape of the visibility curve might be associated with the production of standing

41. Condon, E. U., and Morse, P. M.: Quantum Mechanics, New York, McGraw-Hill Book Company, 1929, p. 166.

42. Heisenberg, W.: The Physical Principles of the Quantum Theory, translated by C. Eckart and F. C. Hoyt, Chicago, University of Chicago Press, 1930, p. 39.

waves within the retinal cones. The recent experiments of Stiles [43] indicating a dependence of the hue of monochromatic light on the angle of incidence of the light on the retina also suggest a photoelectric rather than a photochemical phenomenon. That light entering the eye through peripheral portions of the pupil should appear of lesser intensity than the same light passing through the central pupillary area, as Stiles has also reported, is to be expected if the stimulus is small, since the various aberrations of the eye produce relatively great enlargement of the retinal area stimulated when the point of entrance of the light is peripheral.[44] The relative effect of aberrations of the peripheral portions of the eye will be reduced if the stimulus size is increased. Absorption of light by the pigment epithelium and total internal reflection within the cones have also been suggested [45] as possible explanations of the intensity effect. It is to be noted, however, that the effect is said [46] to be slight at low intensities of retinal illumination at 5 degrees from the fovea. Since aberration, pigment epithelium and total internal reflection are all present at low as well as at high intensities, it seems possible that their effect is not the primary explanation of the phenomenon. Furthermore, a hue shift resulting from a change in the point of pupillary entrance of monochromatic rays can probably not be explained in terms of any of the previous hypotheses if the intensity effect is compensated for so that the Bezold-Brücke effect [47] is not involved. If this hue shift with point of pupillary entrance of the stimulating light can be confirmed and if experiments on aniridic eyes and those with anomalously large pupils show the hue shift to be of considerable magnitude, then the possibility that the initial photopic visual process may be photoelectric should be seriously considered, since attempted explanations of the phenomenon assuming that the initial visual process is photochemical [43] appear to necessitate the postulated existence of different types of cones.

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43. Stiles, W. S.: The Luminous Efficiency of Monochromatic Rays Entering the Eye Pupil at Different Points and a New Colour Effect, Proc. Roy. Soc., London, s.B **123**:90, 1937.

44. (*a*) Jackson, E.: Symmetrical Aberration of the Eye, Tr. Am. Ophth. Soc. **5**:141, 1888. (*b*) Sulzer, E.: La forme de la cornée humaine et son influence sur la vision, Arch. d'opht. **11**:419, 1891; **12**:32, 1892. (*c*) von Brudzewski, K.: Beitrag zur Dioptrik des Auges, Arch. f. Augenh. **40**:296, 1900. (*d*) Pi, H. T.: Total Peripheral Aberration of the Eye, Tr. Ophth. Soc. U. Kingdom **45** (pt. 1):393, 1925. (*e*) Stine, G. H.: Variations in Refraction of the Visual and Extra-Visual Pupillary Zones, Am. J. Ophth. **13**:101, 1930.

45. Wright, W. D., and Nelson, J. H.: The Relation Between the Apparent Intensity of a Beam of Light and the Angle at Which the Beam Strikes the Retina, Proc. Phys. Soc., London **48**:401, 1936.

46. Stiles, W. S., and Crawford, B. H.: Luminous Efficiency of Rays Entering the Eye Pupil at Different Points, Nature, London **139**:246, 1937.

47. Voeste, H.: Qualitätsänderungen der Spectralfarben in Folge von Ermüdung, Ztschr. f. Psychol. **18**:257, 1898.

Finally, there remains the possibility that the shape of the photopic retinal visibility curve is not primarily dependent on the initial visual process but on some subsequent stage in the course of visual perception. Present knowledge of the physiology of nerve is probably insufficient to permit an adequate specific hypothesis to be formulated along these lines. The following analogy is, therefore, intended only to show a conceivable mechanism in which the final sensitivity of the system is independent of its initial process. Assume a photoelectric cell subjected to flashes of light. The flash frequency may be varied, but within wide limits the current developed by the cell is independent of the frequency with which it is excited. Feed the output of the cell into an alternating current amplifier suffering from frequency distortion and measure the output of the amplifier with a suitable alternating current ammeter. The shape of the curve obtained by plotting a graph of meter reading against flash frequency will now be dependent on the nature of the frequency distortion of the amplifier and will be independent of the initial process in the system. Since the frequency of optic nerve impulse appears to vary with intensity,[48] any analogous system capable of accounting for the photopic retinal visibility curve would have to provide symmetric distortion of a modulated frequency. There is some evidence that modulation of optic nerve impulses occurs.

SUMMARY

By applying suitable corrections for the absorption and reflection of light by the ocular media of the human eye a photopic ocular visibility curve is transformed into a photopic retinal visibility curve.

The photopic retinal visibility curve is markedly symmetric, and the data are well represented by a simple probability function.

No photosensitive substance so far found in animal eyes possesses an absorption spectrum shown to correspond to the photopic retinal visibility curve.

The symmetry and smoothness of the photopic retinal visibility curve suggest that it is due to the operation of either a single process or a large number of processes rather than to the operation of three or four processes.

Various possible explanations of the shape of the photopic retinal visibility curve are considered.

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48. (*a*) Adrian, E. D.: The Basis of Sensation, New York, W. W. Norton & Company, Inc., 1928, pp. 53-61. (*b*) Hartline, H. K.: Intensity and Duration in the Excitation of Single Photoreceptor Units, J. Cell. & Comp. Physiol. **5**:229, 1934.

RECENT ADVANCES IN THE CARE OF THE INSENSITIVE CORNEA

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The clinical diagnosis of lesions of the cornea reflects, in its involved terminology, the historical advances in medicine, and a review of the literature shows the chaos that has resulted from the use of descriptive, morphologic, anatomic, neurologic, mycotic and deficiency terms. Staining characteristics and the use of biomicroscopy have not simplified diagnosis nor aided the treatment, which, like diagnosis, is often a matter of individual preference. Duke-Elder's [1] grouping (in his textbook of ophthalmology) of the herpetic, metaherpetic and neuropathic conditions on an etiologic rather than on a descriptive basis has been of aid.

It is with these conditions that the insensitive cornea is primarily associated, although one now sees in increasing numbers secondary corneal lesions as the result of surgical intervention for the relief of trigeminal neuralgia (tic douloureux).

Rose in 1890 was the first to remove the gasserian ganglion successfully after Horsley had tried to section the sensory root, with fatal results. Injections have been used since 1874, and postoperative care is the concern of the surgeon, as Howell [2] reported 26 per cent corneal involvement after injection of alcohol into the gasserian ganglion, while the permanent loss of sensation indicates the need for training the patient in order to avoid loss of sight and disfiguring scars. I have seen a patient with an insensitive cornea wipe his lid so firmly down and out that the edge of his handkerchief touched the cornea. I noticed that the cornea was turned down at the time and have since observed that this is a usual reflex associated with wiping.

The occurrence of insensitive cornea in association with neuroparalytic conditions has caused my associates and me to increase our efforts to find a satisfactory routine which we hope will prove as helpful to others as it has to us. Operation has been performed at the Toronto General Hospital, in the department of neurosurgery, under the direction of Dr. K. G. McKenzie, in over 300 cases of this type in the last fifteen years. A review of this series is now being prepared, in which only 3

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1. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

2. Howell, C. M. H.: Brit. M. J. **2**:786, 1932.

fatalities are reported. The early problems have been dealt with,[3] and an improved technic is available that includes a transtemporal approach and partial section of the sensory roots of the gasserian ganglion. Immediately after operation, a Buller shield is applied over the eye on the side operated on. It is used at night for six weeks after operation, and if at any time the cornea becomes cloudy the lids are sutured together for six months. The patient is fitted with a Tovell shield, described subsequently, for permanent use by day over the cornea on the side operated on and given instructions regarding the washing of the face and the care of the lids. If a red eye should develop, he is asked to report at once. The following written instructions are supplied:

1. Never wash the face except in front of a mirror and close both eyes before putting the hands up to the face.

2. Wear a Buller shield (supplied) at night for two months.

3. No pad or bandage must be allowed to close the lids of the side operated on (on account of the strapping becoming sufficiently loose to allow the lids to open, so that the pad could touch the front of the eye).

4. Avoid dust and wind.

5. Report at once if the eye becomes red, after covering it with the Buller shield.

6. Wear the Tovell shield during waking hours and close the eyes when putting on glasses.

7. Use only boric solution or ointment on the closed lids.

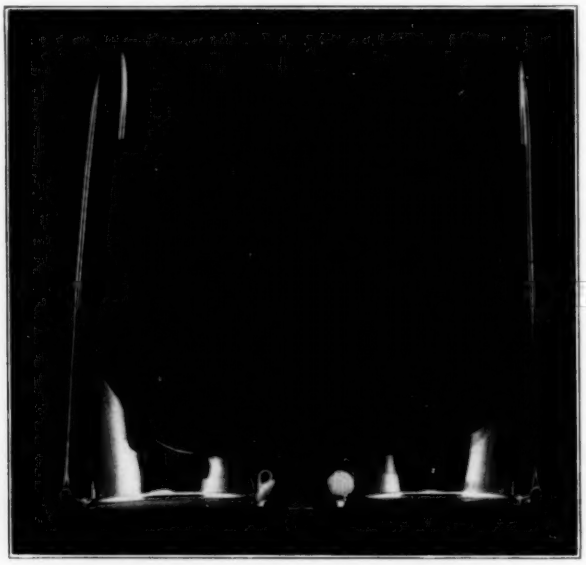
It will be noticed that at no time, according to this latest routine, are the lids bandaged, as in the past it has been found that the cornea has frequently been damaged by the pad when the margins of the lids became separated. Paton [4] has considered the various theories, trophic, antidromic, vasomotor and mycotic, but our experience has been that none of them explains all the conditions causing corneal involvement, and we have proved that if drying and trauma are avoided the cornea is safe. In most of our cases the sensation on the contralateral side has been normal, which insures the winking reflex, but even if both eyes are involved the Tovell shield so controls the ventilation that the formation of droplets of moisture can be regulated and at the same time the danger of trauma is prevented.

In September 1937 Dr. H. M. Tovell, of Toronto, discovered that a medium weight cellophane could be attached to the lens of his glasses to guard against foreign bodies entering his conjunctival sac. Since that time he has, with the help of his optician, developed a protective shield that is firmly clamped between the spectacle frame and a slightly too small, + 3 diopter lens, which he wears for each eye. After the tube of

3. McKenzie, K. G.: Canad. M. A. J. **29**:492, 1933.
4. Paton, L.: Brit. J. Ophth. **10**:305, 1926.

cellophane is clamped between the frame and the lens, the cellophane in front of the lens is removed and the posterior tube is shaped to fit comfortably against the skin, covering the orbicularis muscle; hence it is longest at the temporal side, shorter nasally, still shorter below and shortest of all above. Small holes are drilled in the cellophane above, close to the frame to permit ventilation, and a hinge placed just beyond the longest part of the cellophane permits the bilateral shield to fit in a case.

When this shield was being developed I was consulted by several patients who were suffering from herpes of the cornea, which appeared to be epidemic. They were business men, and although only 2 gave



Tovell eye shield for the insensitive cornea.

a history of being exposed to chickenpox, they came to me at about the same time. They complained of pain, malaise and inability to concentrate and were impatient at the slow course of the disease which kept them from business. The cornea was still insensitive, though staining had ceased to be apparent, and they readily accepted my suggestion to try the inconspicuous Tovell shield. The results were so satisfactory that I extended the use of the shield for patients suffering from insensitivity of the cornea due to any cause. All were more comfortable in the Sahara-like dryness of indoor winter temperature or outside in the wind and cold, and by the use of tinted lenses the glare on snow was reduced.

Recently I saw a patient who had been operated on elsewhere by the cerebellar approach for the relief of trigeminal neuralgia. She had an extensive corneal leukoma and was using a black Doyne occluder. The weight, appearance and movement of this occluder worried her and prevented the use of the left eye, which had vision of 6/60. A Tovell shield was ordered, which permitted her to see well to the left. Ventilation was gradually increased to prevent the formation of droplets, and now she is more comfortable indoors and out and is happy to be rid of the black patch. The inconspicuous appearance of the Tovell shield has made it possible for patients to resume their positions, and it is now used routinely for hospital, as well as private, patients during the period of loss of corneal sensation.

The need for more accurate tests for the sensitivity of the cornea has become apparent. Cotton wool was used at first, but it often touched the lids or lashes and has been discarded. Hairs attached to a scale might permit calibration and quantitative measurements but could hardly be used in a contagious disease. Dr. Solandt, of Dr. Best's department of physiology, measured silk sutures of varying sizes and found a one-in-four variation, the lightest bending at a pressure of about 1 mg. These finest silk sutures, or 50 Denier artificial silk, have been cut to standard lengths and attached with glue to the flat end of a wooden toothpick; they may be kept in a closed test tube and discarded after use.

Bruce,[5] in a recent communication on the treatment of keratitis sicca, remarked on the difficulty of closing the canaliculi by actual cautery, as used by MacMillan. He dissects about 4 mm. of the canaliculus, upper and lower, to block the outlet for tears, with good results. It seems to me that a Tovell shield should be tried when part prevention of drying might suffice. Many of these conditions are temporary, and an operation might be avoided.

In dealing with herpes of the cornea I follow Gundersen's technic.[6] I have not yet had a case of herpes zoster ophthalmicus sufficiently early to use convalescent serum. Gundersen uses whole blood by transfusion or subcutaneous convalescent serum and also peridectomy (syndectomy; peritomy) in keratitis metaherpetica. Gifford[7] recommended the use of 0.5 to 1 cc. of solution of posterior pituitary U. S. P. to relieve the pain of herpes zoster ophthalmicus. Its empiric use was discovered

5. Bruce, G.: Paper read before the Academy of Medicine, Toronto, Canada, March 1939.

6. Gundersen, T.: Tr. Am. Ophth. Soc. **33**:508, 1935; Herpes Corneae, with Special Reference to Its Treatment with Strong Solution of Iodine, Arch. Ophth. **15**:225 (Feb.) 1936; Vascular Obliteration for Various Types of Keratitis: Its Significance Regarding Nutrition of Corneal Epithelium, ibid. **21**:76 (Jan.) 1939.

7. Gifford, S. R.: A Handbook of Ocular Therapeutics, Philadelphia, Lea & Febiger, 1932, p. 125.

by Vandel [8] and Sidlick,[9] and I have found it of great value in relieving the severe neuralgic pain.

Parsons [10] referred to the presence in the cornea of acetylcholine and histamine-like substances, which is an interesting speculation, especially as they seem to be associated with vitamin A.

CONCLUSION

The insensitive cornea must be protected while the condition exists. A practical routine is suggested.

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8. Vandel, S. N., cited by Sidlick.[9]

9. Sidlick, D. M.: Use of Solution of Pituitary in Herpes Zoster, Arch. Dermat. & Syph. **22**:91 (July) 1930.

10. Parsons, J. H.: Diseases of the Eye, ed. 9, New York, The Macmillan Company, 1938.

RELATION OF DRUSEN OF THE OPTIC NERVE TO TUBEROUS SCLEROSIS

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The present study was undertaken in an effort to establish a suspected relation between so-called drusen of the optic nerve and the disorder known as tuberous sclerosis. The occurrence in tuberous sclerosis of drusen-like lesions and the existence of certain similarities in the pathologic picture of the two conditions suggested that the same pathologic process might be responsible for both. Cases of drusen reported in the literature and all cases observed at the Institute of Ophthalmology in the past seven years have been analyzed, and the findings, together with a description of the more important manifestations of tuberous sclerosis, are reported.

DRUSEN OF THE OPTIC NERVE

Drusen, or hyaline bodies, of the optic disk have been described as resembling a conglomeration of frog eggs or tapioca grains or as having a papular surface like a mulberry (figs. 1 and 2). They also appear frequently as waxy, more or less translucent masses, composed usually of conglomerate smaller masses. When these lie beneath the surface of the disk and are not visible or only partially so, ophthalmoscopically they may give an appearance simulating optic neuritis or papilledema (fig. 3). They are usually seen in the disk alone, but when more extensive they may even extend into the retina and forward into the vitreous for several diopters. Occasionally they appear in the retina alone. They are congenital and usually bilateral.

Frequency.—In an extensive form, drusen of the optic disk are rare. In the past seven years only 4 cases were seen at the Institute of Ophthalmology in which the condition was considered sufficiently marked to warrant recording by the art department. Drawings made in 2 additional cases, seen privately, were also secured for study. This number, however, does not give a true indication of the frequency of drusen of the optic nerve. Their occurrence in a less extensive form is not at all uncommon, but the lesions are either so inconspicuous that they are overlooked in clinical examination or they lie below the surface and cannot be seen. In the past seven years 9 cases with hyaline bodies in the disk were encountered in the pathologic department in routine microscopic examina-

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tion of eyes removed for absolute glaucoma (5 cases), malignant melanoma of the choroid (1 case), traumatic detachment of the retina with secondary glaucoma (1 case), buphthalmos (1 case) and hydrophthalmos (1 case). As 893 globes have been examined during this period, the incidence, then, in these cases is approximately 1 per cent. The lesion of the optic nerve was considered to be independent of the other pathologic processes and had in no case been noted clinically, possibly because the interior of the eye could not be seen. This is known to have been true in the case of malignant melanoma of the choroid. The hyaline bodies were seen in the fellow eye, but the disk in the involved eye was not visible.

Figure 1

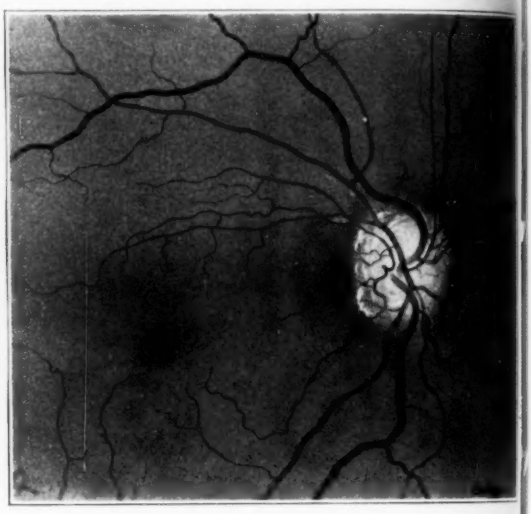

Figure 2

Fig. 1.—Right disk of a woman, aged 48 years, with no symptoms referable to involvement of the central nervous system and no ocular involvement except for the lesions in the optic disks. Vision in the right eye, with glasses, was 20/30. Vision in the left eye, with glasses, was 20/40. Neurologic examination was not done, and the patient was not questioned regarding family history. The right disk was elevated 4 diopters due to a conglomeration of translucent bodies diagnosed as drusen of the optic nerve. The left disk had a similar lesion.

Fig. 2.—Right disk of a youth aged 17, who complained of severe frontal headaches during the preceding year. It was elevated 2 diopters and contained many conglomerate bodies, best shown on the temporal side. Vision with correction was 20/15. The field showed a contraction in the lower nasal quadrant to within 20 degrees of fixation. The blindspot was enlarged. The left disk showed a lesion similar to that seen in the right eye. Vision with correction was 20/30. The field showed a contraction in the lower nasal quadrant to within 30 degrees of fixation. The blindspot was enlarged. A diagnosis of drusen of the optic nerves was made. After two years these lesions have shown progression. Neurologic examination gave negative results. Roentgenograms of the skull were negative. (The patient was a former patient of the late Dr. John M. Wheeler.)

Clinical Course.—In the majority of instances drusen of the optic nerve are harmless and lead to no untoward consequences (fig. 1). Not infrequently, however, the hyaline bodies enlarge gradually and lead to disturbances in vision (figs. 2 and 3). They may even become cystic and

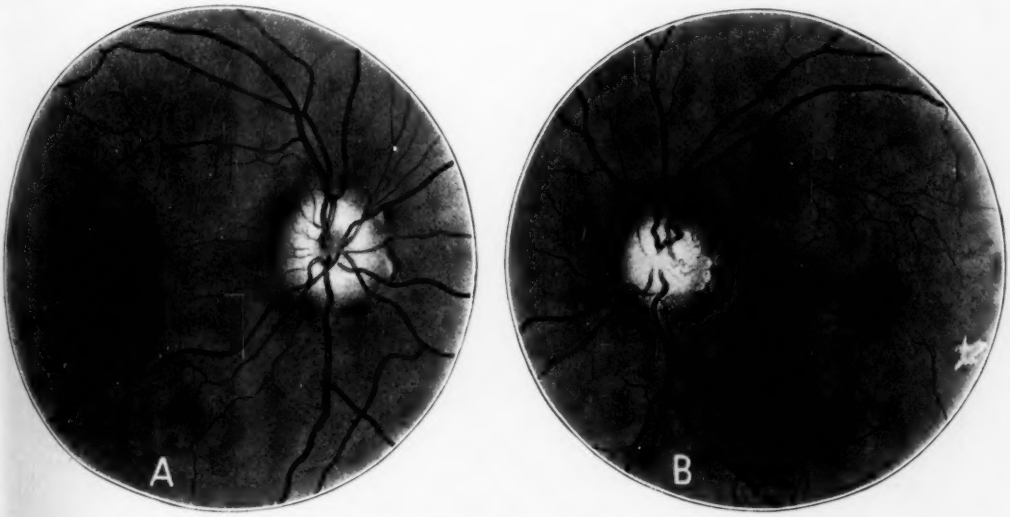

Fig. 3.—*A* and *B*, right and left disks of a boy aged 12 years, who complained of headaches which were occasionally accompanied by vomiting. At one time he was noted as having a peculiar gait and being listless, and sometimes his head would "flop over." He was suspected of having an internal hydrocephalus or tumor of the brain and was investigated from this angle. Examination, including a ventriculogram, gave negative results. Examination of the eyes showed drusen of both optic nerve heads, giving an appearance somewhat resembling papilledema. The central vision was normal. There was constriction of the nasal fields and some enlargement of the blindspots. A remnant of the posterior vascular capsule of the left lens was noted. General examination showed some albumin in the urine and a heart murmur. The patient's condition remained about the same for a number of years, and then he noted a disturbance of vision of the left eye which was found reduced to 20/50. This was due to a hemorrhage on the disk and in the vitreous. There had also occurred some progressive constriction of the nasal fields and enlargement of the blindspots.

At the time of writing this report the patient was 24 years old and in good health. There was no family history of disease of the central nervous system or the eyes. This case is considered one of drusen of the optic nerves showing evidence of subclinical tuberous sclerosis. The right disk (*A*) showed an elevation of 4 diopters and gave an appearance simulating papilledema. On the nasal margin, though, two sharply demarcated bodies projected beyond the margin of the disk. The left disk (*B*) showed an elevation of 4 diopters, and the margins were obscured except on the temporal side. Here the margin extended somewhat toward the macular region and was irregular due to the presence of a yellowish white, waxy-appearing translucent substance. A few small vessels coursed over the temporal surface. (The patient was a former patient of the late Dr. John M. Wheeler.)

rupture into the vitreous or hemorrhage (fig. 3). There is frequently a contraction of the visual fields, which may be progressive, or there may be scotomas (figs. 2 and 3). Central vision may be affected progressively or may vary from time to time. Sometimes there is an associated atrophy of the optic nerve which seems to be out of proportion to that which could be accounted for on the basis of the drusen alone. Lauber commented on how frequently in anatomic examination of eyes with drusen of the papilla there was atrophy of the optic nerve present the origin of

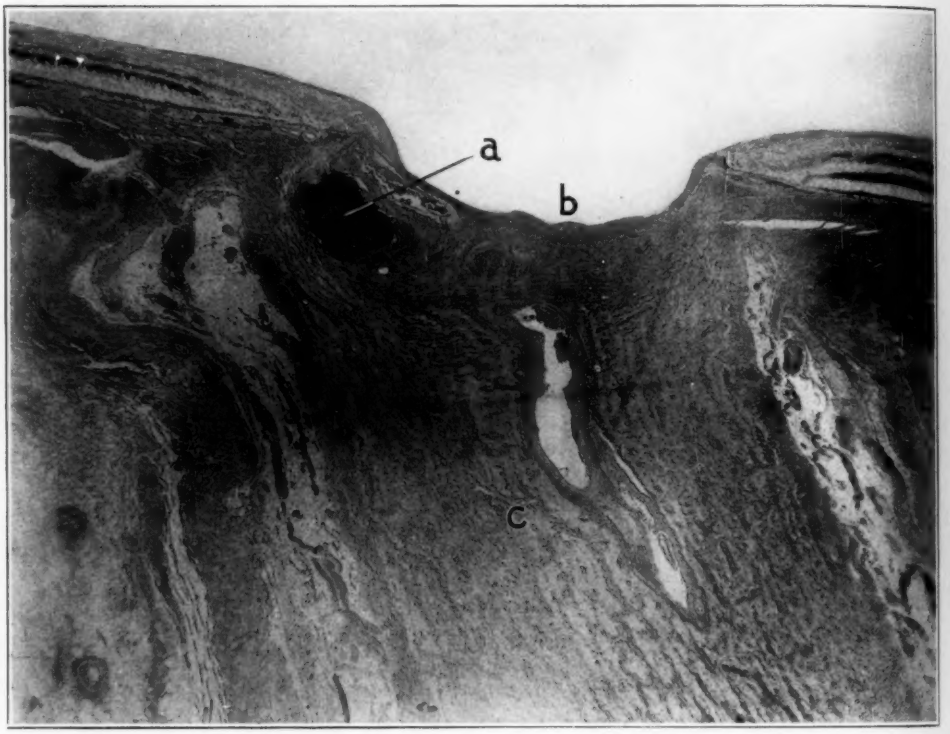

Fig. 4.—Drusen of the optic nerve in an eye removed because of absolute glaucoma. Drusen composed of almost solid calcium are indicated by *a*. Several small daughter areas are seen. Cupping of the disk is shown by *b* and the optic nerve head by *c*.

which was insufficiently explained on local anatomic grounds. Such cases were those of Hirschberg and Cirincione, Gurwitsch, de Schweinitz and Lauber.

Histologic Picture.—Microscopic examination was made in 14 cases of drusen. The lesions usually occupied the nasal side of the disk anterior to the lamina cribrosa (figs. 4, 5 and 7). When extensive, they

sometimes occupied both the nasal and the temporal half, with the greater portion on the nasal side (fig. 6). Situated anterior to the lamina characteristically, they sometimes extended into it but never posterior to it. In 1 instance, however, a separate and smaller focus was noted some distance posterior to the lamina.

The lesions were sharply demarcated with a tendency to be irregularly round, the main mass usually being composed of conglomerate smaller

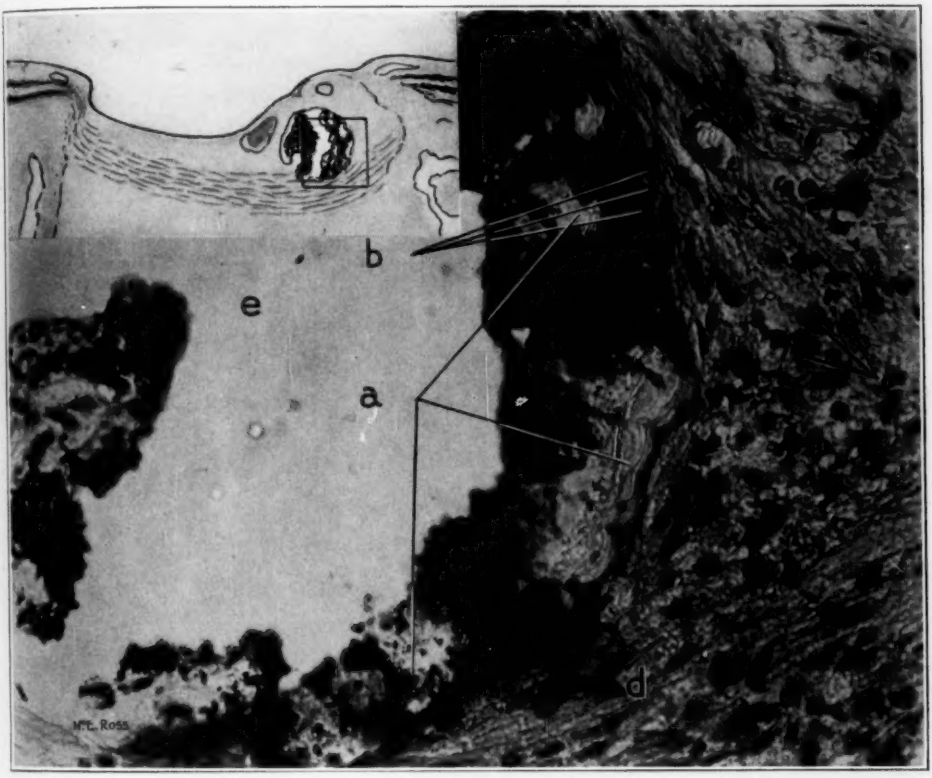

Fig. 5.—High power magnification of a site of drusen of the optic nerve in an eye removed because of absolute glaucoma. Light hyaline areas alternating with the dark calcium areas (the hyalin shows lamellation) are shown by *a*; cells going over to shadow cells and calcification to form part of the main lesion, by *b*; cells in this region showing a refractile hyalin-like substance in their protoplasm resembling that seen in the main lesion, by *c*; lamina cribrosa, by *d*, and cystic space in the center of the area of drusen, by *e*. The insert is a diagram to show the location of the lesion in the nerve. The square designates the site of the high power photomicrograph.

masses with glial septums extending between them (fig. 6). The presence of variously-sized daughter lesions around the main one was

characteristic (fig. 4). Sometimes, however, there were no daughter areas, and the lesion was seen to be sharply demarcated by a thin glial capsule (fig. 7).

The bulk of the lesion was composed of calcium and an amorphous material, which was hyalin or a closely related product (figs. 5, 6 and 7). The tendency to calcium deposition was so marked that the lesion frequently appeared to be almost pure calcium (fig. 4). In some instances the material was composed of various units or separate con-

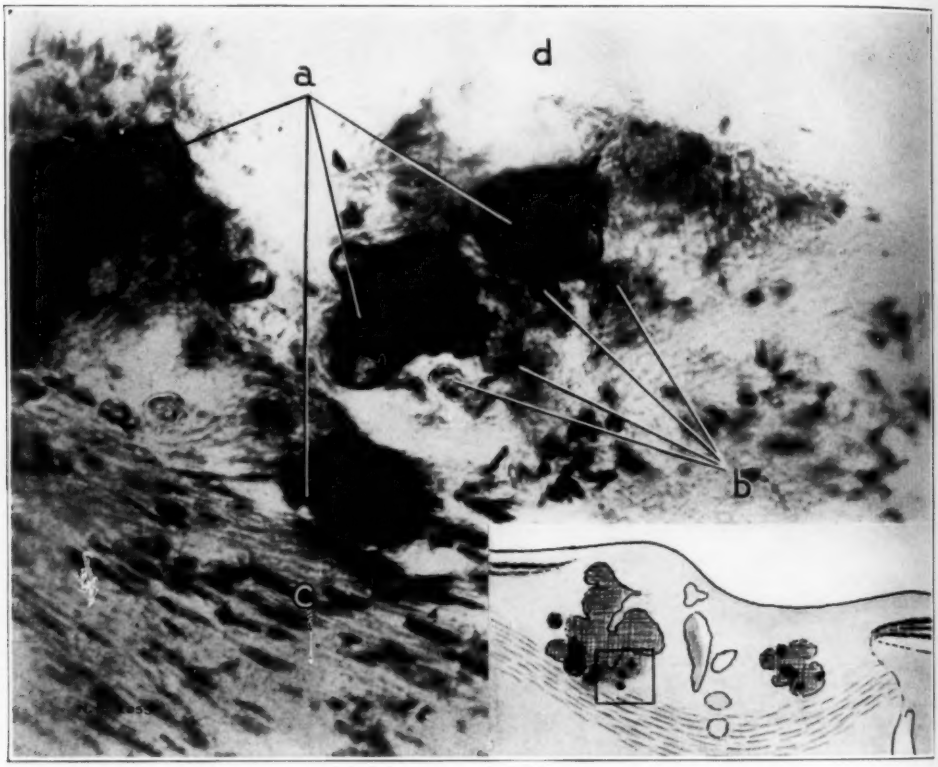

Fig. 6.—High power magnification of a site of drusen of the optic nerve in an eye removed because of a malignant melanoma of the choroid. Foci of calcium showing their formation from the conglomeration of large cells which become shadow cells and then calcified are indicated by *a*; shadow cells becoming calcified and forming part of the main masses, by *b*; lamina cribrosa, by *c*, and cystic space in the center of the area of drusen, by *d*. The insert is a diagram to show the location of the lesions in the nerve. One area is nasal to the central vessels and a smaller area is temporal. The square designates the site of the high power photomicrograph.

glomerate areas, each of them concentrically lamellated around a central focus. In other instances the lamellation was missing, and the lesion was merely a mixture of calcium and a crystalline, or hyalin-like, highly

refractile, stainless substance, which in 1 case showed concentric lamellation (fig. 5) and in another case seemed to be in crystal sheets (fig. 7). These areas of calcium and hyalin-like material were sometimes missing in the central portion of the lesion, giving it a cystlike appearance (figs. 5 and 6). In some instances these holes apparently existed in vivo, but others seemed to be the result of a tendency of the material to drop out of the section in preparation.

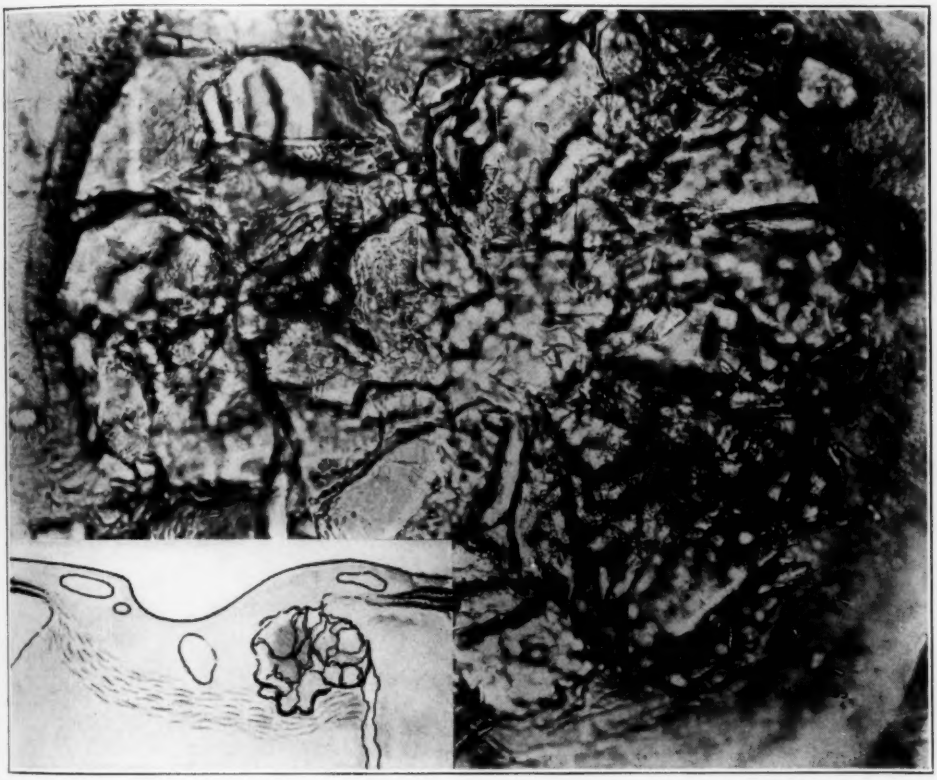

Fig. 7.—High power magnification of a site of drusen of the optic nerve in an eye removed because of absolute glaucoma. This lesion is composed almost entirely of hyalin, and the calcium content is at a minimum. The hyalin in places appears to be in crystal sheets. The insert is a diagram to show the location of the lesion in the nerve.

Cellular elements, absent in some lesions, were to be seen in one form or another immediately around or in the periphery in most lesions. Cells with large oval nuclei, evenly and lightly distributed with chromatin, tended, on entering the lesion, to become shadow cells, then necrotic and finally calcified (figs. 5 and 6). Another type of cell had a large nucleus, a distinct nucleolus and a well demarcated, polygonal-shaped

protoplasm border, and some of these contained a refractile, nonstaining, homogeneous substance like that of the main lesion (fig. 5). Some of the smaller daughter areas resembled calcified cells in that they were round and had a darker calcified central portion corresponding to the nucleus, and inside of this there was a still darker calcified area corresponding to the nucleolus.

This microscopic picture would seem to indicate that the lesions represent a congenital excess of immature neuroglia which undergoes degeneration.

Nature of Drusen of the Optic Nerve.—There has been much speculation as to the nature of so-called drusen of the disk. The earliest

Fig. 8.—Right fundus of patient with tuberous sclerosis showing a typical tumor of the optic nerve and retina (case report). The disk of the right eye was elevated 4 diopters due to the presence of a conglomerated mass of waxy, translucent bodies, giving a nodular mulberry-like surface. A similar lesion was seen in the retina above with an elevation of 6 diopters. There was a lesion in the disk and retina of the left eye similar to the ones in the right eye, except that the latter was located beneath the inferior nasal vessels.

conception was that of Iwanoff and many others, who considered them comparable to the drusen or excrescences of the lamina vitrea. They felt that extension of this membrane into the nerve, or a misplaced fragment of it there, gave rise to the excrescences. Terson felt that they represented a senile change; Streiff, that they resulted from papilledema; Stood, that they were sequelae of optic neuritis; Parsons, that they represented the degenerative changes of an exudate; Lauber, that

they were formed from misplaced pigment epithelial rests, and Corrado, that they belonged to the "heterotopic calcinoses" dependent on parathyroid disturbance.

Associated Systemic Disease.—In most instances drusen are of no consequence locally to the eye, are noted only coincidentally in routine examination and occur in healthy persons. On the other hand, the instances in the literature of patients with associated disease are too numerous to be accepted as coincidental. This is particularly true of associated disorders of the nervous system, which were mentioned in 18 (33 per cent) of 54 cases reviewed in the literature. These were cases reported by de Schweinitz, Fejér, Stood, Niels, Iwanoff, Hirschberg and Birnbacher, Wedl and Bock, Nieden (2 cases), Sachsalber (2 cases), Paderstein, Mendel, Jany, Streiff (2 cases), Lauber and Treitel. Many of the remaining 36 case reports were brief accounts of the condition in the eye and made no mention of the general condition of the patient. It is possible, therefore, that there were more than 18 cases in this group in which there were associated nervous symptoms. Nor does this number include cases in which there were defects of the visual fields, such as hemianopia, probably unexplainable on the basis of the drusen, nor cases in which the atrophy of the optic nerve seemed out of proportion to the lesion of the optic nerve. The commonest neurologic manifestations were convulsions, psychoses, disturbances of gait and speech, hydrocephalus and papilledema.

The next most commonly associated systemic anomaly was renal dysfunction. This was reported as "kidney disease," "kidney trouble" or "Bright's disease" in 7 cases, in 4 of which the patients died of uremia. In none of the 7 was there associated disease of the nervous system. Congenital anomalies of the eye were mentioned in 5 cases: a hyaloid artery, a congenital cataract, a coloboma of the retina, a subluxation of the lens and an anomalous retinal vein. Heart disease was reported in 2 cases.

An unrelated but noteworthy observation is that drusen, or at least drusen-like areas in the optic nerve, occurred in 7 typical and atypical cases of retinitis pigmentosa.

Heredity.—A familial or hereditary tendency toward drusen of the optic nerve is indicated by the reports of Braun, showing the condition to be dominant in 6 members of 2 families; the report of Lauber, showing it to be present in a mother and 2 daughters, and the report of Ancke, who found it in several members of 2 families.

TUBEROUS SCLEROSIS

Bourneville described an anatomic condition of the brain which he noted in young mentally defective persons with epilepsy. He called it "tuberose" or "tuberous sclerosis" because the multiple cerebral areas

of sclerosis resembled a potato, and he felt that it could not be diagnosed clinically. This condition has gradually come to be known as a congenital developmental disorder of an exceedingly protean nature with a heredofamilial tendency. Mental deficiency, epilepsy and adenoma sebaceum (Pringle's disease) characterize it in its pure form, and for this Sherlock has suggested the term "epiloia."

Clinical Course.—According to Critchley and Earl's excellent report, the condition may begin as a developmental delay, particularly in talking and walking. The mental defect may be obvious by the third year and the cutaneous manifestation sometimes in the first decade. At about the second dentition the patient loses ground more rapidly, showing dulness, disordered conduct, emotional outbursts and impaired speech. The epileptic attacks may be of the petit mal, grand mal or jacksonian types, or equivalents. Death often occurs in the second decade from cachexia or status epilepticus.

Cutaneous Complications.—Adenoma sebaceum occurs in tuberous sclerosis as a papular rash, varying in color from reddish to brownish and appearing on the face first in the nasolabial folds and later over the entire nose and over the cheeks in the infraorbital region in a butterfly-shaped arrangement. Other cutaneous lesions which may occur in this and allied diseases are: (1) fibromas, forming coarse, gooseflesh-like areas with a predilection for the trunk; (2) slightly elevated areas of thickening over the skin about the size of the palm and the same color as the surrounding skin, with a predilection for the lumbosacral region and best detected by palpation, and (3) various pigmentary disorders, such as nevi, diffuse bronzing, café au lait patches and areas of abnormal whitening.

I have observed drusen of the optic nerves in a woman aged 26 with a cutaneous lesion of the face resembling adenoma sebaceum.

Associated Systemic Disease.—As part of this disease entity there may be embryonal mixed tumors of the kidney, which are usually multiple and bilateral. According to Critchley and Earl, they occur in 80 per cent of cases and are rarely diagnosed clinically. There may also be multiple rhabdomyomas of the heart, which sometimes lie in the muscle wall and sometimes project into the chambers. Associated tumors have also been noted in the retina, optic nerve, spleen, lungs and breast.

Involvement of the Optic Nerve.—Credit is particularly due to van der Hoeve for first calling attention to the retinal and optic nerve tumors associated with this condition. Characteristically, they are single or multiple, whitish to yellowish tumors, which vary a great deal in size and may reach an elevation of 5 or more diopters. They usually have a nodular or mulberry-like surface and have been described as appearing like a localized accumulation of frog eggs or tapioca grains.

Sometimes the retinal tumors are whitish with a more or less smooth surface. Multiple small white dots or foci are sometimes seen over the fundus, either in conjunction with a localized tumor or in place of it.

Mulberry-like tumors in the disk have been reported by van der Hoeve (4 cases), Nitsch, Kuchenmeister, Bau-Prussakowa, von Herrenschwand, Guillain and Lagrange and Messinger and Clarke. The following case is another of this type:

History.—C. N., aged 14 years, was seen at the Neurological Institute in January 1936. He was an only child, was born at full term and was delivered spontaneously, with no apparent injury. His birth weight was normal. He developed normally, both mentally and physically, until 18 months old. At 9 months he was struck on the top of the head on the right side by the cover of a commode. He was unconscious for from three to four minutes; he did not suffer from convulsions, paralysis or bleeding from any external orifice. When he was 18 months old, while at dinner, the parents noticed that his head turned to the left and that there was twitching of the left upper extremity lasting for from two to three minutes but no unconsciousness. About a month later he had twitching of both upper and lower extremities; this has occurred approximately monthly up to the time of writing this report. Occasionally while walking he falls and has twitching of both upper and lower extremities, incontinence and frothing at the mouth, lasting about two minutes but without unconsciousness. Also, about monthly, he has nocturnal attacks of crying out, followed by unconsciousness and twitching of all extremities, lasting about three minutes and followed by headache and drowsiness. About five or six years ago there appeared a rash on the cheeks with a butterfly-shaped distribution. This is said to have disappeared under treatment by a physician. Associated with the attacks there is usually a great deal of gaseous distention, which is relieved by massaging the back or by belching. The patient is irritable and has temper tantrums, which have been particularly evident during the past five years.

He has frequent headaches, especially in the morning, in addition to the headaches accompanying the attacks. There is no diplopia, no difficulty with hearing, no tinnitus, no olfactory or gustatory hallucinations and no dizziness. The patient was slow in beginning to speak.

He does not suffer from dyspnea with cyanosis or from palpitation. He occasionally has pains in the chest but no chronic cough or hemoptysis.

He occasionally vomits when upset. Gaseous distention, as previously noted, is present. There is no history of hives or idiosyncrasy to any food, but the family thinks that milk, eggs and ice cream predispose to an attack. They have therefore omitted these foods from his diet. He suffers from constipation.

There is no history of genitourinary symptoms.

The patient has had the ordinary childhood diseases with no serious complications. He has never gone to school but has had a private tutor for two hours a day for years. The family states that his memory is good and that he is developing satisfactorily mentally. He does not play with other children.

Physical Examination.—Examination revealed a thin, pale white boy with a macular eruption over the face, the distribution over the cheeks and nose being butterfly shaped. He weighed 127 pounds (57 Kg.), was 66 inches (167 cm.) in height, was of a pyknic habitus and had a light complexion and monotonous speech. He cooperated poorly.

Neurologic Examination.—This examination gave essentially negative results.

Mental Status.—Examination showed the patient to be definitely retarded mentally. He was well orientated. His memory seemed good and insight fair. He talked continuously and foolishly. His intelligence quotient was 42. His chronologic age was 14 years, 9 months and 2 days. The age on the basis of the Stanford-Binet test was 6 years and 2 months and of the Pintner Paterson test, 6 years and 3 months.

Ocular Examination.—Vision in the right eye was 20/15 and in the left eye 20/15. The palpebral fissures were of normal width and equal. No diplopia was elicited. There was no limitation of the movement of the eyes and no nystagmus. The muscles showed orthophoria and a good punctum convergens basalis. The pupils were 3 mm. in size and were round and central and reacted to light and in accommodation and convergence. Corneal sensibility seemed normal. Central color perception was good. The papilla of the right eye and the retina are shown in figure 8. The papilla of the left eye had a lesion similar to one seen in the right eye; the lesion in the retina was similar to one seen in the right eye except that it was located beneath the inferior nasal vessels and measured 1 disk diameter in width and from 2 to 3 disk diameters in length, the long axis paralleling the vessels. The retinal vessels were mainly on the surface of the mass but partially buried within it. The iris was normal. The lens and media were clear. The cornea, conjunctiva and lacrimal apparatus were normal.

Laboratory Examinations.—The Wassermann test was negative. The red and white cell counts and differential count were normal. The morphologic structure, hemoglobin content and index were also normal. The urine was normal except for a trace of albumin. The spinal fluid was normal, including the cell count and the colloidal gold curve. The Wassermann reaction was negative.

Roentgen Examination.—The calvarium was of average thickness. The inner table of the skull presented many small areas of increased density, which were chiefly noted through the superior parietal and posterior frontal region. There was no hypervascularity. On the right side, not far above the corpus callosum and evidently in the rolandic region, there were what appeared to be small flecks of calcification. There was no evidence of increased intracranial pressure. In the edge of the tentorium on the right side, midway between the dorsum and the petrous pyramid, there was a round deposit of calcium. The sella turcica was small but not atrophic, and the basal angle was normal. The air cell development was not remarkable, although the frontal cells were asymmetric, and it is of interest to note that a double suture line passed through the sagittal suture.

Examination of encephalograms after the injection of 75 cc. of air showed a fairly good filling of the ventricles; they were of large average size. The anterior portion of both ventricles, including the bodies as far back as the level of the pineal gland, seemed to fill rather poorly. At this region there was a thinning of both ventricles, due possibly to a large choroid plexus. The occipital horns were well developed. Only a few of the cortical sulci contained air; they were not enlarged.

The esophagus appeared normal; the stomach was medium in position, had a smooth outline and was freely movable. There were no filled defects or incisures noted and no residue of barium sulfate in the stomach at six hours. The duodenal cap filled and emptied normally. The third and fourth portions of the duodenum were large. Apparently the barium entered the jejunum without any undue delay. The ileum and cecum appeared normal, and the appendix was not visualized.

Fluoroscopic examination of the stomach showed the barium passing into the duodenum promptly, but there were rather marked peristalsis and a considerable amount of reverse peristalisis. Films of the abdomen taken every hour failed to show any evidence of obstruction. The large size of the third and fourth portions of the duodenum probably was of no significance.

A single flat film of the abdomen taken twenty-four hours after the ingestion of barium showed most of it to be in the proximal half of the colon, some of it apparently having been expelled.

Diagnosis.—A diagnosis was made of tuberous sclerosis with adenoma sebaceum, tumor of the optic nerve and retina and possible renal involvement.

The multiple foci of increased density and areas of calification noted in the roentgenograms of the skull unquestionably represent the multiple cerebral lesions characteristic of this disease and in which there is a marked tendency for calcium deposition. This finding suggests the value of roentgenograms in diagnosing tuberous sclerosis.[1]

Clinical Variants; Heredity.—Tuberous sclerosis is a heredofamilial condition with many clinical variants and formes frustes and occurs in these abortive forms far more often than in its pure form. This is frequently revealed in a study of siblings and progenitors of patients with the disease. There may be adenoma sebaceum alone or epilepsy or adenoma sebaceum may be combined with epilepsy or with symptoms of cerebral tumor. The cerebral condition may produce focal neurologic signs and raised intracranial pressure simulating tumor of the brain without any of the other usual manifestations. Critchley and Earl reported the case of a girl aged 8 years with headaches, vomiting, defective vision and petit mal attacks. There was papilledema in both eyes. At autopsy the typical changes of tuberous sclerosis were found. Schuster's patient was an epileptic person of normal intellect in whom in early adult life signs of increased intracranial pressure developed. At autopsy there were the usual findings of tuberous sclerosis together with an intracerebral glioma. There may be a visceral tumor alone without mental abnormalities or involvement of the nervous system. Berg's patients were a father and daughter with tuberous sclerosis, both of whom died of primitive renal tumors. The grandfather died after an operation for a renal tumor but during life had shown no evidence of a neurologic disorder. Other patients who had been otherwise normal but under the care of a urologic surgeon for a renal tumor have at autopsy shown changes in the cerebrum typical of tuberous sclerosis.

Typical retinal tumors have also been shown to exist alone, without any other manifestations of the disease, in a member of a family in which

1. After this report was submitted for publication the following article by P. I. Yakovlev and W. Convin was encountered: A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple Brain Stones), Arch. Neurol. & Psychiat. **42**:1030-1037 (Dec.) 1939.

siblings have had typical tuberous sclerosis. Van der Hoeve reported a single typical tumor of this type in the left eye of a woman aged 21, who had no other signs or symptoms but in whose family 5 siblings were found subsequently to be affected with an advanced form of the disease. The patient was seen six years later after she had married. The retinal tumor had enlarged somewhat, and a few smaller ones had appeared. Retinal tumors were found in 3 of her 6 children, and a fourth had numerous epileptic attacks. Koch and Walsh concluded that finding no more than one typical retinal tumor justified a positive diagnosis of tuberous sclerosis.

In 2 instances drusen of the optic nerve have been reported in patients whose immediate family had undefined psychoses: Morten and Parsons reported the case of a girl aged 20 whose mother was in an asylum, and Nieden reported the case of a patient whose family showed a marked hereditary psychosis. It is possible that tuberous sclerosis existed in these families and that drusen of the optic nerve appeared as an abortive manifestation of it in supposedly otherwise normal persons.

Pathologic Picture.—There is general agreement as to the essential features of the pathologic picture of tuberous sclerosis. According to Critchley and Earl, there are numerous whitish, slightly prominent lesions in the cerebral convolutions with no predilection for any one area. These may be from one or two to twenty or thirty in number and may range in size from 0.5 cm. in width and length up to nodules of from 2 to 3 cm. in all dimensions. These lesions may be distinguished from the surrounding cortex by their slightly paler color, or better, by palpation, the firm consistency of the lesions revealing their sclerotic nature. They feel like cartilage and rubber. Palpation may also reveal smaller and darker nodules which have escaped careful scrutiny. Sometimes the nodules degenerate in the center, forming small cysts; more commonly they form calcareous foci. Ordinarily, only the cerebral hemispheres are affected, but the cerebellum, medulla, spinal cord and retina are occasionally involved. In the walls of the third and lateral ventricles small irregular projections are also noted; these usually arise from the thalamus and are located immediately beneath the ependyma.

Microscopically, these sclerotic zones show a considerable overgrowth of glial cells and their processes. Some curious large cells foreign to the mature nervous system are also present. They seem to be immature and embryonic cells approximating the neuronic or the glial cell types. Outstanding features of the lesions are a marked tendency toward calcium salt deposits and the formation of hyalin. The blood vessels may be considerably dilated, even approaching sinusoid proportion, and there may be a tendency to hyaline degeneration of the vessel walls. In a case of tuberous sclerosis Messinger and Clarke were able to examine

microscopically an eye which showed the typical mulberry-like lesion of the disk. The pathologic picture was the same as that found in the cases of drusen of the optic nerve encountered in the pathologic department, except that in addition to the calcium there was some bone formation.

Van der Hoeve expressed the belief that tuberous sclerosis, multiple neurofibromatosis (Recklinghausen's disease), Hippel-Lindau disease and the Sturge-Weber syndrome are all related and have the same underlying pathologic process, the characteristic manifestations of each depending on the site involved. Tuberous sclerosis involves the cerebrum, multiple neurofibromatosis the cranial, peripheral and sympathetic nerves, and Hippel-Lindau disease, the cerebellum, medulla and spinal cord. Van der Hoeve also expressed the belief that they are all congenital heredofamilial anomalies, the principal signs of which are cutaneous lesions, tumefaction and cysts, combined with other congenital malformations in various parts of the body and especially in the central nervous system. There may be spina bifida, ectopia testis and syndactyly. In all conditions nevi or nevoid growths play a prominent role. Darier called adenoma sebaceum "naevi vascularies verrugeux;" Pasini held a similar view, and Jacobi expressed the belief that the condition represents nevi in which the glands of the skin proliferate. Van der Hoeve suggested calling the entire group the "phakomatoses" (phakos—mother spot).

CONCLUSIONS

The findings in this study indicate that drusen of the optic nerve are a feature of the congenital developmental anomaly known as tuberous sclersois. They may appear as a part of the fully developed protean disease but more frequently are seen as one of its many clinical variants or formes frustes. This conclusion is based on (1) the similarity of the pathologic process in the two conditions; (2) the occurrence in typical cases of tuberous sclerosis of lesions in the optic nerve which have the identical clinical appearance of so-called drusen of the optic nerve; (3) the occurrence in one third of the cases of drusen of disorders of the nervous system which are consistent with those encountered in tuberous sclerosis; (4) the congenital heredofamilial tendencies of both conditions, and (5) the association of renal disorders and congenital anomalies with both conditions.

If this conclusion is correct, drusen of the optic nerve assume new significance as a familial developmental defect which is frequently associated in the patient, in his progenitors, in siblings or in offspring with serious involvement of the central nervous system and, rarely, with renal and cardiac lesions.

Furthermore, in view of the frequency with which drusen are encountered coincidentally in pathologic specimens, it may be assumed that their incidence, in an inextensive form, is considerably greater than is generally believed, and from this, in turn, it is reasonable to suppose that similar changes may occur in the brain far more frequently than is generally recognized.

Mr. N. E. Ross did the technical work and supplied the photomicrographs; Miss Lilly Kneiske gave assistance.

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DISCUSSION

DR. FERDINAND KOCH: Dr. Reese's paper lends emphasis to a point that might be made here. There is a tendency from time to time, as

noted in the literature, for certain diseases and lesions of uncertain or unknown causation to be grouped under broad, convenient generic headings.

One such categoric term is phakomatosis, meaning "mother spot." It implies the presence of embryonal cell rests which manifest themselves later as new growths. It has been suggested that the disease entities of the Sturge-Weber syndrome, Recklinghausen's neurofibromatosis, Hippel-Lindau angiomatosis and tuberous sclerosis all might readily be grouped as phakomatoses because of the apparent clinical common denominator of somewhat similar cutaneous lesions seen in these four diseases.

It is barely possible that justification for this grouping exists on clinical grounds. Micropathologically, however, this grouping is much more open to question. Assigning dissimilar entities to a single category probably should not be encouraged unless justifiable proof exists for doing so or unless a working hypothesis is desired for investigative purposes.

The grossly manifest clinical differences exhibited by the diseases just mentioned may be illustrated briefly by a few slides. [Slides were shown.] The first depicts a child with a rather extensive naevus flammeus and buphthalmos of the right eye. This is the Sturge-Weber syndrome. The second slide depicts some of the many lesions seen in Recklinghausen's disease. Exophthalmos, tumor of the lid and a café au lait-pigmented spot are shown. A slide of the changes seen in the angiomatosis of Hippel and Lindau was not available.

The next few slides depict tuberous sclerosis. The obvious cutaneous lesions of adenoma sebaceum are presented by the young lad in his teens, shown in this picture. The roentgenogram of the head depicts the increase in intracranial pressure together with numerous intracranial tumors with early calcification. The type of tumor mentioned by Dr. Reese is depicted in another slide, but in this instance it appears in the retina and not in the disk and is associated with secondary atrophy of the optic nerve subsequent to increased intracranial pressure with choked disks. The next slide shows a second retinal tumor situated below and temporal to the one previously shown. The irregularly distributed whitish dots represent additional, numerous small tumors. The last slide is a view of a retinal tumor in the upper periphery of the left eye.

Entities so dissimilar clinically and so protean in their individual manifestations, as was shown briefly by the slides, probably should not be grouped together if for no other reasons than that further investigative work tends to be delayed and the correlation of probable associated factors may be passed over.

Dr. Reese, however, has investigated some hitherto overlooked factors and has presented a new and most interesting point of departure for the consideration of the causation and relational occurrence of drusen of the optic disks. His findings strongly suggest a definite interrelation of these lesions to tuberous sclerosis. The microscopic similarity of the lesions lends support to his thesis, while the clinical evidence may be considered confirmatory.

The effect on the patient of drusen of the optic disks compared with that of tuberous sclerosis differs only in degree. The former pursues

an essentially slowly chronic or even subclinical course, while the latter is relatively rapidly progressive and ultimately fatal.

Routine, carefully critical and analytic ophthalmoscopic and micropathologic examinations might result in raising the figures for the incidence of drusen of the disks and yield information and material of investigative value. It would be of interest to employ differential stains on specimens obtained from young subjects in whom drusen, as seen with the ophthalmoscope, have not existed sufficiently long to have become calcareous or hyalin like. It is in such specimens that it will be possible to determine whether or not the cellular components of drusen of the disk are related to, or are similar to, the partially undifferentiated glial and neuronal cells known to comprise the tumors of the retina and the disk in tuberous sclerosis.

DR. MILTON TARLAU: With the exception of van der Hoeve, who did not employ differential staining technic, all previous investigators who studied the tumors of the optic nerve and retina occurring in tuberous sclerosis were agreed that these tumors are primitive gliomatous neoplasms. Grinker, however, although he did not have the opportunity to study a tumor personally but reached his conclusions from the published descriptions and photographs, suggested more specifically that the tumors are astroblastic neoplasms of low growth potentialities.

About a year ago Dr. McGrath and I had the opportunity of studying such a tumor. The patient was under observation both before and after the development of a tumor of the optic nerve, and we obtained the globe for pathologic studies after death. Differential staining showed the presence of glial fibrils and the absence of neurofibrillae, so that there can be no doubt as to the gliomatous nature of the neoplasm. In addition, we were fortunate in obtaining a section with a capillary cut tangentially. Coming from the tumor cells on either side of the capillary were typical perivascular feet, characteristic of the astroblastic glial series. Thus we were able to prove definitely, I believe for the first time, that these tumors are astroblastomas and to verify Grinker's ideas.

In the slides illustrating the histologic studies in the cases presented by Dr. Reese can be seen a number of intact cells. These bear a striking morphologic resemblance to the astroblasts of the better known tumors of the retina and optic nerve occurring in definite cases of tuberous sclerosis. In addition, the latter are characterized by cystic spaces, some of which may be filled with hyaline material, and they occasionally show calcified inclusions, as in the case of Messinger and Clarke, cited by Dr. Reese. While it is of course true that there is an urgent need for careful histologic study with differential staining, the evidence at hand certainly suggests that Dr. Reese's tumors are also astroblastic neoplasms of low growth potentialities and that they are at least related to, if not identical with, the manifestations of tuberous sclerosis.

MALIGNANT MELANOMA—SO-CALLED SARCOMA—OF UVEA

III. EXTENSION INTO THE OPTIC NERVE

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Malignant melanoma does not involve the optic nerve frequently. Its relation to the optic nerve is of clinical importance, however, because the growth can extend along the nerve into the cranium. In a series of 94 cases of malignant melanoma the neoplasm had invaded the optic nerve in only 12 instances.[1] Similarly, Byers and MacMillan[2] from their own cases and from the literature found 40 instances of extension into the optic nerve in 392 cases. The relative infrequency of this complication (10 to 13 per cent) suggests that the optic nerve and the retina, especially the nerve fiber layer, are not "fertile soils" for the growth of the neoplasm. Yet it is commonly thought that melanomas of the skin and choroid frequently metastasize to the central nervous system. In discussing this point of view, Wortis and Wortis[3] reported 6 cases of metastasis to the brain at the Bellevue Hospital. Of these, involvement of the choroid was noted in 4 instances. In 1 case the optic nerve sheath was involved, but the mode of extension from the eye to the brain, whether by direct growth along the nerve or by metastasis through the blood stream, was not stated.[4]

Malignant melanoma may originate in the choroid or elsewhere in the body to reach the optic nerve through direct extension or by metastasis through the blood stream. It may originate also in the optic nerve.[5]

The growth of the melanoma originating in the choroid may extend into the optic nerve by two possible routes, along the retina or into

1. Terry, T. L., and Johns, J. P.: Am. J. Ophth. **18**:903, 1935.

2. Byers, W. G. M., and MacMillan, J. A.: Tr. Am. Ophth. Soc. **33**:184, 1935.

3. Wortis, H., and Wortis, S. B.: Metastatic Melanoma Involving Central Nervous System, Arch. Neurol. & Psychiat. **36**:601 (Sept.) 1936.

4. In reply to an inquiry concerning these cases, Dr. Herman Wortis reviewed his material. He wrote that in case 2 the tumor definitely extended along the nerve from the eye. In case 6 there was again definite involvement of the optic nerve, and he was of the impression that the neoplasm had extended back from the eye, but he lacked absolute proof.

5. Levine, J.: Primary Melanosarcoma of Optic Disk, Arch. Ophth. **14**: 229 (Aug.) 1935.

the optic nerve directly from the choroid. To invade the retina directly, the malignant melanoma from the choroid must penetrate the lamina vitrea and the pigment epithelium of the retina.[6] Before this penetration, however, the lamina vitrea has given sufficient resistance to cause a variable amount of lateral spread of the tumor, giving rise to a somewhat flattened growth. When the lamina vitrea is penetrated, the head of the tumor grows through the opening rapidly to spread out laterally as well, thereby producing the typical rounded head, the constricted neck and the broad, somewhat flattened base. The conclusion that the neoplasm grows rapidly after penetration of the lamina vitrea is based on the observation that few tumors show a small undeveloped head, whereas many tumors show a large well formed head. Through the medium of toxins or other chemical products of the tumor, through altered circulation or through direct pressure the cells of the pigment epithelium of the retina usually overlying the apex of the tumor are stimulated to proliferate and often become adherent to the retina proper. The neoplasm extends across this bridge of adherence into the retina. Even after this stage, widespread involvement of the retina is not the invariable result. In fact, the retina, although frequently penetrated, only rarely is invaded over a large area, but when the neoplasm has the potentiality to grow in the retina, it spreads extensively. The lack of a good blood supply, the scarcity of mesodermal structures in the retina, the physical arrangement of the tissue or some other protective mechanism must be responsible for the infrequency of widespread retinal invasion.

Malignant melanoma can extend into the retina from the ciliary body and iris after reaching the ciliary epithelium. It is possible that the neoplasm originating in the choroid near the ora serrata could grow forward within the ciliary body and even within the iris to invade the retina more or less around the anterior edge of the lamina vitrea.[7]

From the retina the tumor usually reaches the optic nerve by direct growth, but it must be borne in mind that metastasis to the optic nerve is possible, not only from the retina and the choroid but from some other part of the body. In the pathologic laboratory of the Massachusetts Eye and Ear Infirmary one eye which contained a malignant melanoma primary in the iris showed an extremely small area of metastasis into the ciliary body near the root of the iris separate and distinct from the tumor of the iris. Kreibig [8] pointed out that metastasis

6. Metastasis through the blood to the retina from the choroid is in the realm of remote possibility through cilioretinal or opticociliary vessels.

7. It must be remembered, however, that only the elastic portion of the lamina vitrea plays out in the posterior part of the corona ciliaris, whereas the cuticular lamina continues to the root of the iris.

8. Kreibig, W.: Ztschr. f. Augenh. **87**:265, 1935.

of malignant melanoma into the eye does occur. He not only referred to cases in the literature but reported additional ones. Kreibig also suggested criteria by which he differentiates primary neoplasm from metastasis. To stress the point that malignant melanoma may metastasize to the eye, he cited instances of metastatic carcinoma and hypernephromas in the globe. Dunphy and I reported a case in which carcinoma had metastasized to the optic nerve.[9] Cushing and Eisenhardt [10] reported an instance of meningioma having invaded the eye from the orbit (a case first studied by Verhoeff). It is conceivable that a malignant melanoma may metastasize to or extend to the optic nerve from structures other than the eyeball, although there appear to be no examples in the literature. Were statistics available, the ratio of the frequency of metastatic carcinoma of the eye to that of carcinoma in general might indicate the frequency with which malignant melanoma originating elsewhere in the body may metastasize to the eye. It is my opinion that metastasis of malignant melanoma to the eye and especially to the optic nerve is rare and is present only when generalized metastasis has occurred, in which event the liver is likely to be involved.

The neoplasm from the choroid can enter the optic nerve by extension past the free edge of the lamina vitrea at the optic nerve head. In this event it must penetrate the border tissue, the relatively dense connective tissue lining the so-called intraocular canal of the optic nerve. Although malignant melanoma often invades the choroid on all sides of the nerve head, direct penetration into the optic nerve is not frequent. Of 8 cases in which the posterior segment of the eye contained malignant melanoma which had extended into the optic nerve, the tumor grew through the border tissue in only 2, whereas the neoplasm reached the nerve through the retina in 6.

The mode of extension to the brain may be along the optic nerve itself or along the intervaginal space. In 5 instances the extension of the neoplasm was limited to nerve tissue only, but in 4 cases both the nerve and intervaginal space were involved. In 1 case only the meninges and the nerve were involved the same distance behind the eye. Even in this case the amount of tumor involving the meninges was small, while the nerve itself, largely destroyed by the tumor, was heavily invaded and increased to 4.5 mm. If these few cases were representative, then it can be said that the route by which the neoplasm reaches the brain is primarily in the substance of the nerve itself and not along the meninges.

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9. Terry, T. L., and Dunphy, E. B.: Metastatic Carcinoma in Both Optic Nerves Simulating Retrobulbar Neuritis, Arch. Ophth. **10**:611 (Nov.) 1933.

10. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938, p. 287.

It is a serious misfortune to cut the optic nerve too short, leaving malignant cells in the nerve central to the neurectomy. To illustrate the gravity of this situation, the following cases are reported.

CASE 1.—M. M., a 50 year old woman, had glaucoma in each eye. Because the intraocular pressure was not controlled by means of miotics, a trephine operation was done on each eye, with uneventful convalescence. Three years later the intraocular pressure became very high in the right eye, and a large bulging mass was present in the region of the previous operation. The eye was enucleated

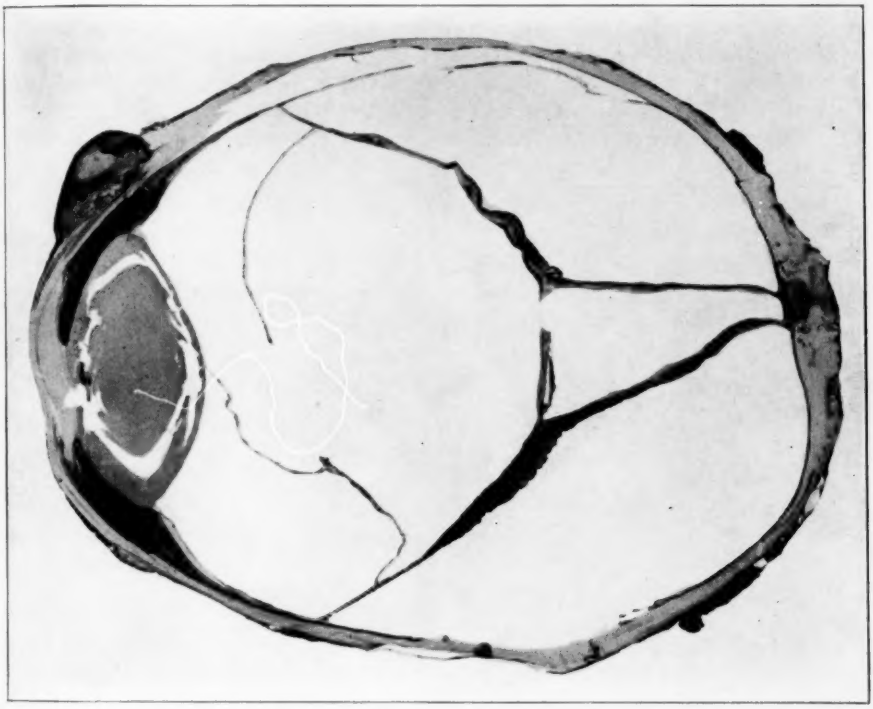

Fig. 1 (case 1).—Malignant melanoma of the iris with extension to the optic nerve along the ciliary body and the retina. The growth fills the shallow glaucomatous cup and invades the optic nerve itself even behind the lamina cribrosa. The neoplasm also has extended along the tract of a trephining operation to produce an episcleral nodule.

by Dr. Elwood T. Easton and sent to the pathologic laboratory of the Massachusetts Eye and Ear Infirmary.

After the globe was fixed in a 10 per cent dilution of formaldehyde for twenty-four hours and a 2.5 per cent solution of hydrochloric acid for twenty-four hours, it was opened. Sections for microscopic study were prepared by the pyroxylin method and stained with hematoxylin and eosin.

The essential lesion was a malignant melanoma of the iris (fig. 1) containing epithelioid and spindle B cell types (Callender [11]). Melanotic pigment was

11. Callender, G. R.: Tr. Am. Acad. Ophth. **36**:131, 1931.

relatively scarce. Many mitotic figures were present. The neoplasm had extended along the tract of the operative wound to the episcleral tissue, where an extraocular nodule some 3 by 5 mm. in size had developed. The iris was infiltrated extensively by the growth, and there was a layer of tumor cells on both its anterior and its posterior surface. The ciliary body was also heavily infiltrated. The tumor had extended along the surface of the ciliary body, largely destroying the ciliary epithelium to reach the retina itself. The invasion of the retina appeared to be chiefly in the region of the retinal vessels, as if the neoplasm were spreading along a perivascular space (fig. 2). In places all layers of the retina were involved. The growth extended from the retina into the optic nerve itself through the lamina cribrosa. The intervaginal space was not involved.

After the enucleation the patient appeared to be free from symptoms for four and one-half years, when she began to lose weight. During six months she lost 36 pounds (16 Kg.). She complained of failing vision in the left eye and of headaches. The right orbit was filled with an irregular mass associated with edema and redness of the eyelids. Although the intraocular pressure in the left

Fig. 2 (case 1).—Infiltration of the tumor along blood vessels. It appears that the retinal extension has been largely along perivascular spaces.

eye was normal and the trephine opening still appeared to be functioning properly, temporal hemianopia was present. The patient was referred to the neurologic service of the Massachusetts General Hospital, where it was concluded that the malignant melanoma had extended along the optic nerve to the chiasm, thus destroying the crossed nerve fibers and producing the hemianopia. Later, complete loss of vision resulted from further destruction of the chiasm by the growth. The nature and extent of the neoplasm made further operation ill advised. The patient died seven years after the enucleation from the intracranial extension.

Case 2.—J. M., a 55 year old man, entered the outpatient department of the Massachusetts Eye and Ear Infirmary in the service of Dr. E. B. Dunphy in October 1932, with a complaint of blurred vision in the right eye which had increased progressively for one and one-half months. Associated with this was intense supraorbital pain.

The vision in the right eye was found to be reduced to projection of light only, while vision in the left eye was normal. The right pupil was somewhat larger than the left. In the fundus of the right eye there was a large separation of the retina, which reached almost to the equator below, nasally and temporally.

Although the peripheral part of the separated retina appeared clear, as if subretinal fluid were present, the main mass of the separation was dark, consistent with the presence of a pigmented neoplasm beneath the retina. Several posterior synechiae were present. The eye did not transilluminate well posteriorly and below, the reduced transillumination reaching forward to the equatorial region. A diagnosis of malignant melanoma of the choroid was made, and three days later the eye was enucleated.

After the globe was fixed in a 10 per cent dilution of formaldehyde for forty-eight hours and a 2 per cent solution of hydrochloric acid for twenty-four

Fig. 3 (case 2).—Malignant melanoma of the choroid with massive extension along the optic nerve.

hours, it was opened. A heavily pigmented, rounded choroidal neoplasm was found projecting from the posterior segment. The neoplasm, 12 mm. high and 18 mm. wide, covered the nerve head. Sections for microscopic study were prepared by the pyroxylin method and stained with hematoxylin and eosin. Some were bleached before staining.

The angle of the iris was blocked by a moderately broad anterior peripheral synechia, and Schlemm's canal on one side was filled with blood. The iris was heavily pigmented. On the surface of the iris over a small area was a delicate newly formed vascularized membrane. The ciliary body was compressed. The neoplasm extended over the optic nerve head as a large somewhat pedunculated mass. The greater part of the tumor was so heavily pigmented that the individual

cells could not be seen, but at the periphery where the melanotic pigment was much less the tumor cells could be distinguished clearly as large, slightly elongated spindle cells. Study of bleached sections showed that the cell type in the heavily pigmented region was the same. The neoplasm, which contained many blood spaces, had penetrated along emissaria into, but not through, the sclera in several places. The deepest penetration had reached a point two thirds of the distance through the sclera. The tumor had invaded and largely destroyed the retina surrounding the papilla, had filled the glaucomatous excavation of the nerve head and had penetrated the lamina cribrosa to invade the optic nerve itself (fig. 3). On one side the intervaginal space was also invaded, but the extension backward was limited to the nerve.

After the pathologic study, the patient was recalled to the clinic. On unsuccessful search was made for evidence of metastasis, and a posterior exenteration of the orbit was done four months after the enucleation. The lids were not removed. Dr. V. H. Kazanjian reconstructed the orbit, enabling the patient to wear a prosthesis, with relatively good cosmetic results.

Twenty-seven months after the enucleation the patient returned to the clinic complaining of severe weakness and inability to stand for a long period. He felt he would fall whenever he turned his head quickly. A study of the visual field of the left eye revealed the presence of a temporal hemianopia. The patient was referred to the neurological service of the Massachusetts General Hospital, where a diagnosis was made of intracranial extension of the malignant melanoma into the optic chiasm with destruction of the crossed fibers. The tumor was not operable. Twenty-one days after the patient was discharged from the hospital he died.

Extension of the neoplasm into the nerve should be suspected in all cases of intraocular malignant growth, especially when the tumor is near the disk. At the time of enucleation the surgeon may observe involvement of the nerve if heavy pigmentation is present in the cut end or if the size of the nerve is increased noticeably. Final proof of penetration of the optic nerve rests with the findings of the pathologist. So much time is consumed in the usual routine preparation of sections of an enucleated eye that the discovery of neoplasm in the optic nerve most probably would be made too late to eradicate the tumor completely by removing the stump of the optic nerve or even by removal of the orbital contents.

A careful examination of the patient for evidence of general metastasis and intracranial extension should be conducted before any operation is done. An enlarged liver is presumptive evidence that general metastasis has occurred. Dawson [12] expressed the belief that melanuria is indicative of invasion of the liver. Wortis and Wortis [3] found that the most common symptoms of intracranial involvement are the manifestations of increased intracranial pressure, including headaches, vomiting, dizziness and symptoms suggestive of meningoencephalitis. They found xanthochromic spinal fluid indicative of melanin pigment or melanoma cells in the spinal fluid itself. To these findings one should add temporal

12. Dawson, J. W.: Edinburgh M. J. **32**:501, 1925.

hemianopia of the uninvolved eye arising from destruction of the crossed fibers in the optic chiasm in view of the cases herein reported.

If a long enough piece of optic nerve is removed at the time of enucleation, recurrence in the orbit or extension into the cranial cavity can be prevented when the optic nerve is invaded by a malignant melanoma. As simple as this treatment appears, it cannot be carried out invariably, because the neoplasm may have extended along the nerve into the optic foramen before the enucleation is done. If clinical evidence of involvement of the optic nerve is present at the level of the neurectomy, a diagnosis easily and quickly proved by means of frozen sections, an exenteration of the orbit should be done. It is not enough to remove only a longer piece of nerve, because the instrument used to cut the optic nerve at the original operation may have spread viable tumor cells to other parts of the orbit. In a relatively healthy patient whose life expectancy is several years, one should not stop with an exenteration of the orbital contents if the nerve is involved over a considerable extent. In that event the intracranial and interosseous portions of the optic nerve can be removed.[13]

How much optic nerve should be removed at enucleation? If it is known that no neoplasm is present in the optic nerve, then the neurectomy can be done very near the eye with safety. If one bears in mind that over 40 per cent of the intraocular malignant melanomas are not even suspected at the time of enucleation,[1] then one is impressed even more with the importance of removing a long piece of nerve with the eye routinely. Removing a long piece of nerve does not seem to make the convalescence or the end results after enucleation less satisfactory. The use of a clamp or hemostatic scissors on the nerve not only controls hemorrhage but facilitates the subsequent removal of a longer piece of nerve after the globe is freed.

CONCLUSIONS

1. Malignant melanoma originating in the eye or in the optic nerve can extend into the cranial cavity along the nerve.

2. Malignant melanoma can reach the optic nerve by the following routes: (1) from the choroid by extension along the retina, (2) by direct extension into the optic nerve through the border tissue of the intraocular canal of the optic nerve and (3) by metastasis.

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13. The removal of intracranial and interosseous portions of the optic nerve was done at my suggestion on a patient with an extension of a retinoblastoma into the optic nerve. Dr. Jason Mixter, of the Massachusetts General Hospital, found it a relatively easy procedure, although he thought an attempt to remove a part of the chiasm with the nerve would be an extremely difficult procedure. This case probably will be reported in detail later.

3. The neoplasm appears to grow toward the brain more readily along the nerve itself than along the intervaginal space and the meninges.

4. Intracranial extension gives rise to increased intracranial pressure with a defect in the temporal field and later blindness of the uninvolved eye.

5. Intracranial extension can be prevented by removal of a sufficiently long piece of nerve, which may include the interosseous and intracranial portions of the nerve.

6. Exenteration of orbital tissue must be done if there is any possibility that viable tumor cells have been spread through orbital tissue at the time of the original operation.

CORNEAL INVOLVEMENT IN CONGENITAL ICHTHYOSIS (KERATODERMA)

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CINCINNATI

A recent article by Cordes and Hogan [1] dealt with ichthyosis of the skin and described a case in which corneal involvement of pannus-like nature was associated. The lesion covered the lower three fifths of the cornea, was sharply demarcated from the normal cornea above by a slightly raised, irregular border and passed interruptedly into the conjunctiva and sclera below. Vascular loops arising from the anterior ciliary and conjunctival vessels were a prominent feature. Severe and persistent photophobia and lacrimation were distressing symptoms.

From a study of this case and a brief analysis of the literature they concluded:

> Involvement of the ocular tissues in cases of ichthyosis of the skin is rare and may occur in several forms:
>
> (*a*) There may be asymptomatic involvement of the cornea in the nature of dystrophy of the corneal cells and nerves. This form is seen only with the slit lamp or other means of magnification.
>
> (*b*) There may be an inflammatory form, showing smooth or papillary hyperplasia of the conjunctiva, with involvement of the cornea due to mechanical irritation, which causes secondary changes.
>
> (*c*) The cornea may be involved primarily by a keratosis in which the scales correspond to the scales present in dermatologic lesions.

Their report is noteworthy because, besides that of Buller,[2] which on careful study does not reveal itself as pertinent since the case reported probably was one of vernal catarrh, it is the only one to be found in the English language. Cases reported in the foreign literature are rare. Only one of these has been studied from a histologic point of view. This was discussed by Verryp and will be gone into in more detail later. Almost all authors mention the disturbing and persistent symptom of photophobia. In a few instances ectropion has been a stubborn com-

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1. Cordes, F. C., and Hogan, M. J.: Ocular Ichthyosis: Report of Case, Arch. Ophth. **22**:590 (Oct.) 1939.

2. Buller, F.: A Rare Form of Ophthalmia Granulosa Associated with Ichthyosis, Tr. Am. Ophth. Soc. **4**:582, 1887.

plication due to secondary scar tissue contraction, leading in turn to the usual corneal lesions seen in such event.[3]

To the slowly growing literature on the association of ocular and cutaneous diseases, Richner [4] added a report on the occurrence of superficial epithelial changes consisting of whorl-like or dendritic figures in the cornea of a patient with hereditary keratosis of the palmar and plantar areas. He collected 4 similar cases from the literature and referred to analogous corneal lesions in cases of keratosis follicularis spinulosa decalvens, as reported by Siemens, Wessley and others.

REPORT OF A CASE

K. V., a white boy, was first admitted to the Children's Hospital on Feb. 10, 1932, at the age of 2, with a diagnosis of rhinitis and mild rickets. No attention apparently was paid to the eyes or to the mother's history that the boy had suffered severely with photophobia since he was 1 year old. On Jan. 23, 1933, he was referred to the ophthalmologic clinic of the Children's Hospital because of the photophobia the boarding home mother said that he had had since August 1932, when she first got him. The eyes watered continuously, and the child could stand no light. At that time a diagnosis of subacute conjunctivitis was made and a mild collyrium prescribed. He was not seen again until the following year, at which time tonsillectomy and adenoidectomy were performed. He was followed in the clinics from time to time, chiefly for rhinitis and coryza. Pustular dermatitis was diagnosed at the dermatologic clinic, and cutaneous tests for food and inhalant sensitivity gave negative results. The true condition was not recognized at the opthalmologic clinic, and the child was lost from observation.

On Jan. 9, 1939, when the boy was aged 9, he was observed as a private patient, and at that time, in addition to the photophobia and lacrimation, which were always better in summer and had been present since infancy, corneal lesions were found which were believed to have caused his symptoms. They consisted of scattered grayish white, well circumscribed, elevated nodes, averaging 1 mm. in diameter and obviously superficial. They were more numerous in the right than in the left cornea and were particularly numerous in the upper portion of each cornea. Curiously enough, there was no ocular congestion seen.

Because of the great blepharospasm and photophobia, even after cocainization, a more careful study could not be made. The vision with correction was 20/100 in each eye. The boy kept his head down, with his chin on his chest, and resisted efforts to open his lids for determination of his vision. When his eyelids were thus forcibly opened, streams of tears poured from his eyes and nose. It was noted that the skin of his body and extremities, including his scalp, was dry and scaly. The skin about the nares and corners of his mouth was cracked and excoriated. A diagnosis of allergic keratitis was made, and the patient was referred to the Children's Hospital for thorough investigation. All the laboratory tests, including cutaneous sensitization tests, gave negative results, except for evidence of a mild secondary anemia. The attending dermatologist,

3. Löhlein, W., in Schieck, F., and Brückner, A.: Kurzes Handbuch des Ophthalmologie, Berlin, Julius Springer, 1931, vol. 3, p. 305.

4. Richner, H.: Corneal Lesions in Hereditary Palmar and Plantar Keratoma, Klin. Monatsbl. f. Augenh. **100**:580, 1938.

Dr. Leon Goldman, diagnosed the cutaneous condition as congenital ichthyosis. A search of the ophthalmic literature for information regarding similar cases revealed that reported by Verryp, whose patient was greatly benefited by excision of the nodes. Therefore, on March 18 Dr. Everett Muir, then senior resident in ophthalmology at the Cincinnati General Hospital, operated on the right eye. With the edge of a keratome knife, five grayish white, slightly elevated nodes, irregular in size and shape, were peeled from the central corneal area. A similar node was removed in a like manner from the lower nasal margin. The denuded area was painted with a 1 per cent solution of silver nitrate, and an ophthalmic ointment containing metaphen (1 : 3,000) was instilled. Recovery was uneventful. The photophobia persisted, and on May 5 Dr. A. A. Levin, attending ophthalmologist at the Children's Hospital, removed most of the nodes from the left cornea. He was discharged with the cornea healing well. Large doses of vitamins A and D were prescribed, and a mild collyrium was used locally. A decided local and general improvement was found to be present on June 27. The photophobia, except in very bright light, had disappeared, and the skin, although moderately scaly in unexposed places, was more nearly normal. Since the patient had usually shown improvement during the summer, this could not necessarily be attributed to the treatment. It was, however, possible to examine his eyes more carefully. The cornea in each eye showed a few nodes which had either not been removed or else had developed since the operations. These were elevated, oval white lesions scattered here and there in the corneal epithelium, surrounded by areas of diffuse corneal haze and associated with a few fine superficial blood vessels arising from the limbus. Fine radiating criss-cross lines in the stroma were seen with the corneal biomicroscope, but it could not be determined if these were nerves or not, although the impression obtained was that they were not nerves. The vision in the right eye had improved to 20/70 and in the left eye to 20/50.

The patient was seen again on September 23, and his condition had continued to improve. The vision in the right eye was 20/50 and in the left eye 20/40, and for the first time in his life he was able to enter and continue school. Photophobia was present only in very bright light. Lacrimation had ceased, and along with it the nasal discharge and cracks in the skin about the nostrils. Local and general treatment had been continued.

At the time of the last examination, on December 2, the general improvement was found to have continued. The mother reported that the boy's school work was progressing well, and although the skin was scaly this was obviously the best winter he had ever had. There was a psychogenic side to the photophobia, in that as long as nothing was said about the sensitivity to light he kept his eyes open. He was able to stand ordinary focal illumination but not the light from the slit lamp. There was nothing new seen in the corneas. Both corneas showed white elevated nodes, more discrete in the left. The vision was 20/40 — in each eye.

The bits of tissue removed from each cornea were fixed in a 10 per cent dilution of formaldehyde U. S. P. and sent to the Holmes Ophthalmic Laboratory, Cincinnati, for study and report by Dr. Mary Knight Asbury, ophthalmic pathologist.

The following observations were made:

The specimens from the right cornea consisted of several tiny bits of tissue. The largest were curled up. Microscopically, the tissue resembled that in another case in which a diagnosis of corneal dystrophy of the Salzmann type was made. The epithelium was very irregular in width, frequently only two cell layers thick. Where the epithelium was thinnest, Bowman's membrane was apt to disappear, and the corneal lamellas were thick, granular, poorly defined and palely staining

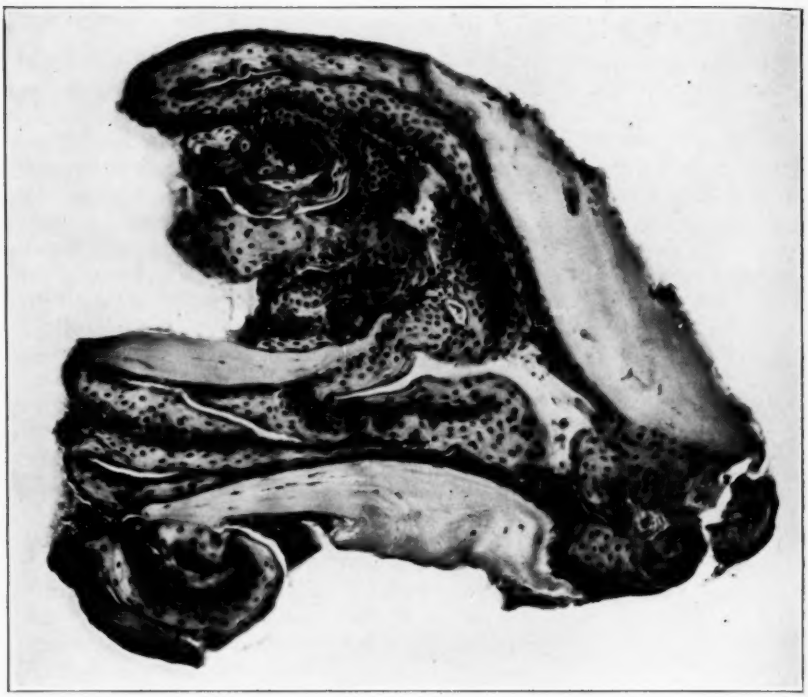

Fig. 1.—Ichthyosis corneae. Nodule from the right cornea.

Fig. 2.—Ichthyosis corneae. Nodule from the left cornea.

and the nuclei were scarce. No hyaline deposits were seen, and no inflammatory reaction was present (figs. 1 and 2). The pieces from the left cornea were even smaller than those from the right eye and consisted of folded epithelium to which clung a few shreds of corneal lamellas or Bowman's membrane. The epithelium appeared to be extremely irregular in width, usually thickened. There were a few wandering cells seen in one tag of corneal stroma.

Because of the similarity of the histologic picture in this case and in one of Salzmann's corneal nodular dystrophy observed in the ophthalmic clinic of the Cincinnati General Hospital,[5] a few comments

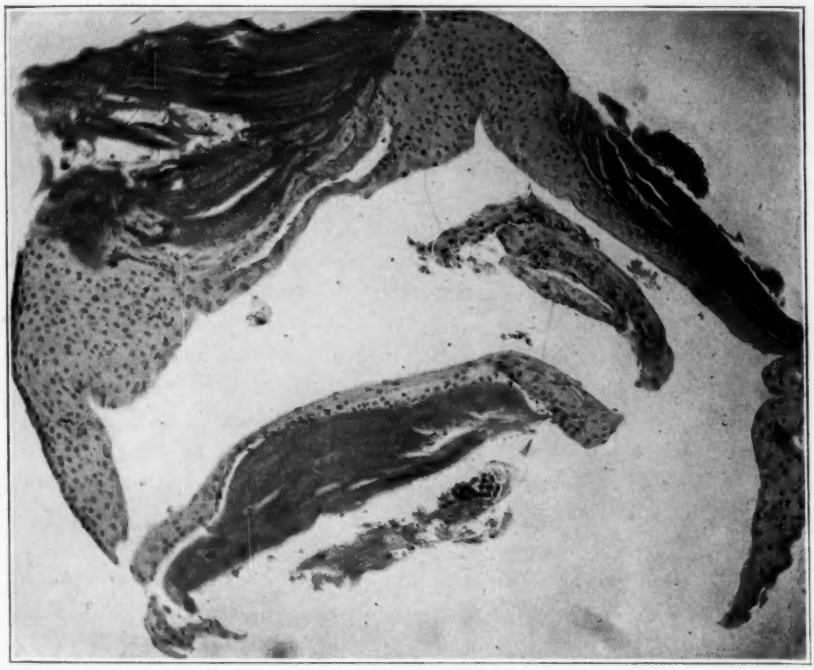

Fig. 3.—The confluent nodules from the cornea of a patient with Salzmann's corneal dystrophy.

on the examination of tissue in the latter case by Dr. Asbury may be suggestive. The patient was a man of 54 years of age. The corneal lesions began in the left eye when he was 2 years of age and in the right eye at least fifteen years ago. It had progressed in spite of treatment. Microscopic study of the nodules (fig. 3) showed an irregular thickness of the epithelium of the cornea. Where the epithelium thickened a suggestion of Bowman's membrane could be seen and the corneal lamellas

5. Muir, E.: Salzmann's Nodular Corneal Dystrophy, Am. J. Ophth. **23**:138, 1940.

distinguished. The main body of the nodule was homogeneous except for occasional islands of pale, swollen nuclei. There was no inflammatory infiltration to be found.

REVIEW OF THE LITERATURE

A review of the available literature disclosed 2 cases of ichthyosis corneae similar in every respect to the case of ichythyosis here reported. In 1 case, that of Ischreyt,[6] there were white, sharply defined, opaque nodules projecting from the surface of the cornea. Ischreyt [6] expressed the belief that the cutaneous scales were analogous to those of the cornea. The other case, that of Verryp,[7] is worthy of reporting in more detail. The central area of each cornea of a 12 year old boy, suffering from congenital ichthyosis, showed small, gray, elevated opacities, some of them scales, located in the epithelium primarily, with light cloudiness of the parenchyma. He complained of constant photophobia, dry scaly skin and thin cilia and his body showed generalized ichthyosis. Microscopically, the tissue showed cornified epithelium, with indistinct cell borders, subepithelial swelling of the corneal stroma and scattered defects in Bowman's membrane. The removal of the superficial layer of the cornea favorably influenced photophobia. Verryp pointed out the close relation between this condition and that of keratosis cornea (Komoto), dyskeratosis cornea (Spanlung) and apparently nodular degeneration as described in some cases.

SUMMARY

A 9 year old boy with congenital ichthyosis had multiple corneal nodules, which histologically resembled those seen in Salzmann's corneal dystrophy. Removal of most of the nodules and large doses of vitamins (especially D) favorably influenced the severe photophobia and also his cutaneous condition, which had persisted since infancy. A similar case was found in the literature. Several authors, among them Kraupa,[8] Verryp [7] and Groenow,[9] pointed out the similarity between this condition and other corneal dystrophies, especially the Salzmann type, but the entire subject awaits further investigation.

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6. Ischreyt, G.: Ocular Inflammation Resulting from Ichthyosis, Jahresb. ü. d. Leistung d. Ophth. **39**:407, 1909.

7. Verryp, C. D.: Ichthyosis Corneae? Klin. Monatsbl. f. Augenh. **80**:830, 1928.

8. Kraupa, E.: Familiar Cellular (Ichthyoitc) and Neurotic Dystrophy of the Cornea, Klin. Monatsbl. f. Augenh. **73**:229, 1924; The Familial Degenerative Corneal Dystrophies (Neurotic Dystrophy and Ichthyosis Corneae) in the System of the So-Called Dystrophies of the Cornea, ibid. **70**:396, 1928.

9. Groenow: Keratosis (Ichthyosis), in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1930, vol. 14, pt. 1, p. 129.